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OF THE

CHEMICAL LABORATORY

Biological
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OF THE

AMERICAN MEDICAL ASSOCIATION

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ANNUAL REPORTS

OF THE

CHEMICAL LABORATORY

OF THE

AMERICAN MEDICAL ASSOCIATION

VOLUME 11

JANUARY–DECEMBER, 1918

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PREFACE

The Chemical Laboratory of the American Medical Association was established in 1906 to assist the Association's Council on Pharmacy and Chemistry in the investigation of proprietary and unofficial nonproprietary medicinal preparations offered to the medical profession.

In accordance with the principles of its foundation, the Laboratory of the American Medical Association concerns itself primarily with the examination of those proprietary and unofficial medicinal preparations which the Council has under consideration. The Laboratory determines whether the claims made for the composition of these preparations are truthful, and establishes standards whereby the identity and purity of remedies admitted to the Council's publication "New and Nonofficial Remedies" may be determined.

In addition to the investigations made for the Council on Pharmacy and Chemistry, the activities of the Laboratory are directed in many other lines. It aids THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION in supplying the medical profession and the public with information about the character and composition of drugs. When requested, it reviews and verifies the chemical data contained in editorials and original contributions. It is often called on for information as to the character and composition of quack treatments and so-called "patent medicines." Through the columns of THE JOURNAL, and through direct correspondence, it responds to requests of physicians with information regarding the composition of medicines which they prescribe or in which they are interested. During the past year the Laboratory has devoted a large part of its time to work carried out at the request of the Committee on Synthetic Drugs of the National Research Council, and other war-time activities.

This volume contains accounts of those portions of the Laboratory's activities which are of interest to workers concerned with the examination and standardization of medicines. Special attention is called to the reports on the American-made synthetic drugs: acetylsalicylic acid, procain, bismuth tribromphenate, barbital, phenylcinchoninic acid and phenetidyl-acetphenetidin hydrochlorid. It is hoped that these studies may be an incentive to manufacturers toward the elaboration of definite standards for the drugs which they manufacture.

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PART I

REPRINTS OF CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION

EXAMINATION OF AMERICAN-MADE ACETYLSALICYLIC ACID

Paul Nicholas Leech, Ph. D.

Reprinted from the Journal of Industrial and Engineering Chemistry, Vol. 10, No. 4, page 288, April, 1918

At the request of the Council on Pharmacy and Chemistry, the A. M. A. Chemical Laboratory has undertaken examinations of American-made synthetic drugs. The most extensively used synthetic is acetylsalicylic acid and hence an investigation of this product was deemed expedient.

For seventeen years acetylsalicylic acid was protected by a United States Patent (the proprietors were not given a patent in other countries) and sold under the name "Aspirin." In February, 1917, the patent expired, and since then a number of firms have engaged in the manufacture of acetylsalicylic acid, selling it either as such or as aspirin, modified, of course, by a distinctive firm designation. During this period the former manufacturers (The Bayer Co., New York, in past years called Farbenfabriken of Elberfeld Co., New York) have been extensively advertising, both to physicians and the public, the alleged superior qualities of their product. The chemical examination, therefore, was concerned chiefly with tests of purity, and the comparison of the American brands with the formerly patented product.

In European countries, acetylsalicylic acid[1] is described in the various pharmacopoeias as a condensation product of acetic anhydrid or acetyl chloride with salicylic acid (*o*-hydroxybenzoic acid). Generally the test of identification is hydrolysis of acetylsalicylic acid and qualitative tests for acetic acid and salicylic acid. For purposes of purity the requirements are essentially that the specimen should have a certain melting point, should show absence of salicylic acid by means of ferric chlorid (the manipulations for the tests are variously described) and leave no appreciable ash. The two tests of purity most generally employed, however, are the melting point and the reaction with ferric chlorid.

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[1] Unfortunately, the nondescriptive name "aspirin" has been used extensively in European literature, and has even gotten into European pharmacopoeias, instead of the scientific name "acetylsalicylic acid."

MELTING POINT

The melting point of acetylsalicylic acid has been given at various temperatures from 118 to 137 C.,[2] the British Pharmacopoeia describes the melting point at 133 to 135 C.; the German Pharmacopoeia "about 135 C.;" the French Pharmacopoeia at 135 C.; New and Nonofficial Remedies, 1917, 134-136 C. The Bayer Company, in the patent trial at Chicago a number of years ago, gave among the "four infallible tests" a melting point of "about 135 C." Several men have carefully determined the melting point in recent years. Emery and Wright[3] in 1912 found that "Aspirin, Bayer" melted at 130.5-131 C. In France, François[4] has determined the melting point of pure acetylsalicylic acid, which, according to his method, is 132 C. When various samples of acetylsalicylic acid were examined in this laboratory, it was found that the melting point of none was as high as that described in New and Nonofficial Remedies or the British, French, or German pharmacopoeias when taken according to the general method of the U. S. Pharmacopoeia, Vol. 9, p. 596. On critical observation, it may be seen that the melting point of acetylsalicylic acid is preceded and accompanied by decomposition. If the sample in the melting tube is heated from the original room temperature of the bath to 120 C., the temperature of melting will be lower than if the bath is first heated to 120 C. and the melting-point tube then placed in the bath.[5] Thus the melting point of acetylsalicylic acid, like so many organic compounds which decompose and do not melt sharply, is unsatisfactory and cannot be taken as an "infallible test" of purity, especially when determined by different operators who do not give their method in detail. After making a large number of melting-point determinations of acetylsalicylic acid, alone and in parallel with other operators, it was decided to use the method described in the U. S. Pharmacopoeia modified by first heating the bath to 120 C. before attaching the melting-point tube to the thermometer.

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[2] For reference to older literature see Beilstein, II, 1496 (889).

[3] "The Melting Temperature of Aspirin and Salicylic Acid Mixtures."
Proc. Assoc. Off. Agr. Chem., 1912; Bureau of Chemistry, Department of Agriculture, Bull. 162.

[4] Assay of Aspirin, J. pharm. Chim. **15**: 213, No. 7, 1917.

[5] Similar observations were made by Emery and Wright, who state: "An accurate determination of the melting temperature in this way (the rate of heating was such as to give a rise in temperature of about 1 degree per minute) is rendered difficult by the fact that 'aspirin' decomposes on heating, as evidenced in the depression of the melting temperature of the pure substance of about 1 degree for every five minutes' heating just below its melting temperature."

The melting point of purified acetylsalicylic acid was found to be 131.5-132.5 C. (corr.).[6] With the exception of one specimen, which was obviously impure, the various specimens examined melted between 128 and 133 C. as may be seen in the accompanying table. It would appear that this range of melting points would be more acceptable and reliable than the melting points described in various standards.

PRESENCE OR ABSENCE OF FREE SALICYLIC ACID

It is generally conceded that the presence of salicylic acid in amounts more than traces is deleterious. Furthermore, the amount of salicylic acid is a good index of the purity of the acetylsalicylic acid, because the test is so delicate that, under favorable conditions, mere traces may be determined and, as a rule, the better the product, the less the amount of free salicylic acid.

The tests appearing in various pharmacopoeias for salicylic acid as an impurity in acetylsalicylic acid do not give concordant results, different workers interpreting the results differently, nor are they detailed in such a manner as to yield maximum delicacy.

After experimentation, it was decided to establish a "limit" test of approximately 0.1 per cent. free salicylic acid, when carried out according to the following method:

0.1 g. of the substance was placed in a dry colorimeter tube and 1 c.c. of alcohol,[7] previously distilled over NaOH, was added. After the acetylsalicylic acid had dissolved, 48 c.c. of water and 1 c.c. of fresh 0.1 per cent. ferric chloride ($FeCl_3.6H_2O$) solution were added. At the same time a control was run by treating 1 c.c. of a "standard" salicylate solution the same as above.[8] If within two minutes the color given by the acetylsalicylic acid is not more intense than the color given by the "standard," the presence of not more than 0.1 per cent. free salicylic acid[9] is proved.

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[6] Isolated crystals attached to the walls of the melting-point tube, apart from the bulk of acetylsalicylic acid, melted at a lower temperature.

[7] An excess of alcohol destroys or lessens the color when only a very minute amount of salicylic acid is present.

[8] The control should be made each time, as standing in the air changes its tinctorial power.

The solutions used were prepared as follows:

Redistilled alcohol was treated with a small amount of sodium hydroxid for twenty-four hours, then again distilled.

The color standard was made by dissolving 0.116 gm. of dried sodium salicylate in water, adding 1 minim of glacial acetic acid, and making up to 1,000 c.c. Each c.c. represents 0.1 mg. of salicylic acid.[10]

The ferric chlorid solution was made by diluting 1 c.c. ferric chlorid ($FeCl_3.6H_2O$) test solution U. S. P. with 99 c.c. of water. The diluted solution must be freshly prepared each day.

With one exception, all of the commercial specimens examined responded satisfactorily to the foregoing test showing less than 1 part salicylic acid in 1,000 parts acetylsalicylic acid. The individual results are given in the accompanying table.

OTHER TESTS

New and Nonofficial Remedies, 1917, requires that acetylsalicylic acid shall form a clear solution with warm sodium carbonate solution; that sulfates, chlorids and heavy metals shall be absent; that 0.5 gm. shall leave no weighable ash. All the brands reported in this paper complied with these requirements.

So far there has been no satisfactory quantitative estimation of acetylsalicylic acid. True, various methods have been proposed, but they are objectionable. It was thought that hydrolysis of acetylsalicylic acid and then titrating the solution by comparing the color formed by ferric chlorid with that of a standard control might yield interesting results, providing that the conditions were alike. For this purpose 1 gm. of acetylsalicylic acid was dissolved in 10 c.c. of alcohol and diluted to 1,000 c.c. The solution was then heated at 98-100 C. for two hours, allowing the alcohol to evaporate, then allowed to stand at room temperature (22

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[9] The presence of pure acetylsalicylic acid does not seem to affect the iron (Fe^{+++}) salicylic acid coloration. The small amount of acetic acid was added to the sodium salicylate control solution (1) to simulate an acidity approximating the acidity of the acetylsalicylic acid, and (2) since acetylsalicylic acid gives by hydrolysis both acetic acid and salicylic acid, it was thought advisable to add acetic acid to the standard. If there is any free acetic acid in a sample of acetylsalicylic acid containing salicylic acid (which I believe is generally the case when salicylic acid is present) then it would modify the color given by the same amount of salicylic acid alone. For this reason it was thought to be more comparable to have the standard contain a slight amount of acetic acid.

[10] This standard is somewhat similar to the one proposed by T. W. Thoburn and Paul J. Hanzlik, J. Biol. Chem., 23, 175.

C.) for twenty-two hours. After adding water sufficient to make 1,000 c.c., it was compared colorimetrically for salicylic acid strength. The amount of hydrolysis varied so with different samples under the same conditions, that it was realized that an approximate assay by this method was unreliable. If the assay were made under more exact conditions, quantitative comparisons might be possible. In one experiment, after 60 days the hydrolysis of the acetylsalicylic acid was 61 per cent. which is in rough agreement with the work of Tsaklatos and Horsh.[11]

MELTING POINT AND SALICYLIC ACID DETERMINATIONS

Brand	Melting Point Corrected	Free Salicylic Acid Colorimetrically
Acetylsalicylic acid, P. W. R.[1].	130.0-131.0°	Colored, but showing less than 0.1 per cent.
Acetylsalicylic acid, Millikin[2].	130.0-131.0°	No color
Acetylsalicylic acid, Millikin[2] 5-grain capsules	129.0-130.0°	No color
Acetylsalicylic acid, Millikin[3] 5-grain capsules[5]	128.0-129.0(*a*) 125.5-126.5°(*b*)	Colored, but showing less than 0.1 per cent. (*a*) Considerably more than 0.1 per cent. (*b*)
Acetylsalicylic acid, Squibb[2]..	131.0-132.0°	No color
Acetylsalicylic acid (Aspirin),[1] Monsanto	131.0-132.0°	No color
Acetylsalicylic acid, M. C. W.[1]	130.5-131.5°	Colored, but showing less than 0.1 per cent.
Acetylsalicylic acid, M. C. W.[1]	131.5-132.5°	Colored, but showing less than 0.1 per cent.
Acetylsalicylic acid, M. C. W.[1]	131.0-132.0°	Colored, but showing less than 0.1 per cent.
Aspirin, Bayer[1] (before patent expired)	131.5-132.5°	No color
Aspirin, Bayer[1, 4] (after patent expired)	128.5-129.5°	Colored, but showing less than 0.1 per cent.
Aspirin, Bayer[1, 4] (after patent expired)	129.5-130.5°	Colored, but showing less than 0.1 per cent.
Aspirin, Lehn and Fink[2]......	130.5-131.5°	0.1 per cent.
Aspirin, Lehn and Fink[2]......	130.5-131.5°	Colored, but showing less than 0.1 per cent.
Aspirin, Lehn and Fink[1]......	131.0-132.0°	Colored, but showing less than 0.1 per cent.

1. Obtained on the open market.
2. Obtained from manufacturer.
3. One-third of the capsules (a) contained a white powder; two-thirds of the capsules (*b*) contained a pink powder having strong odor of acetic acid and not complying with the tests.
4. Not described in "New and Nonofficial Remedies, 1917;" the other products are.

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11. Apoth. Ztg., 1915, p. 247; Bull. soc. clin.; **17:** 401 (1915). "Studies of the decomposition of aspirin determined by titrametric methods and by conductivity measurements indicate that the reaction is exceedingly complex.—" T. and H. Chem. Abst., **10,** 591.

DISCUSSION

Apart from the proposed revision of the standards for the melting point and limit of salicylic acid in acetylsalicylic acid, the examination shows that there is no appreciable difference between the various brands of acetylsalicylic acid examined, all of them with one exception (acetylsalicylic acid, Milliken, 5-grain capsules, purchased on the open market) complying with the tests described in this paper. The Journal of the American Medical Association, in past years, has protested repeatedly against the monopoly given to the Bayer Company for their "Aspirin," contending that acetylsalicylic acid (aspirin) was not new, and that "Aspirin, Bayer" was simply a good brand of acetylsalicylic acid which could be bought in foreign countries at much lower prices than here. Although the patent in the United States has expired, "Aspirin, Bayer" is still being retailed at higher prices than other products which are now enjoying the privilege of American manufacture.

Mr. Paul Bakewell,[12] in an opinion answering the warning circular of the Bayer Co. in reference to the use of the word "aspirin" by firms other than Bayer, argues very ably that acetylsalicylic acid, before the patent was granted, meant the impure substance which was not used therapeutically, while "aspirin" was designated as the improved product (a new article of manufacture, the particular acetylsalicylic acid made under the Hoffman patent) and "is the substance now known in pharmacy as aspirin" (statement made by an officer of the Farbenfabriken of Elberfeld Co. in U. S. Circuit Court, 1909). The products reported in this paper are (with the one exception) the same as described in the Hoffman patent, and, in the sense of Mr. Bakewell's argument, are "aspirin." However, it would seem better if the name acetylsalicylic acid, instead of aspirin, were used, especially by physicians in their prescriptions because (1) it is a generic, scientific name; (2) "Aspirin, Bayer" is sold at higher prices than other products, whereas chemically equivalent products sold under the descriptive name may be purchased at a lower price. Finally, the manufacture of acetylsalicylic acid in this country is another example of the fact that American chemists can produce the drug synthetics, and at the same time make products as good as, if not better than, those of German origin.

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[12] "In the Matter of Aspirin, Answer to the warning circular of the Bayer Co. of June 1, 1917," by Mr. Paul Bakewell, Monsanto Chemical Works.

Addenda

Shortly after the above work was published, the Journal commented editorially as follows:

ACETYLSALICYLIC ACID, OR "WHAT'S IN A NAME?"

Under the caption "What's In a Name?" the current (April) issue of the *Journal of Industrial and Engineering Chemistry* has an editorial dealing with the nomenclatures —common and proprietary—of acetylsalicylic acid. The editorial was prompted by an article by Dr. Leech printed in the same issue. Replying to its own question:

> "The answer to this question in so far as it applies to acetylsalicylic acid (popularly known as aspirin) is the difference between eighty-eight cents, the price the druggist must pay for every one hundred tablets of Bayer aspirin, and forty cents, the cost of an equally pure American product. Naturally, this difference in cost is passed on to the individual consumer.
>
> "That no scientific justification exists for this difference in cost is clearly shown in the contribution by Dr. Paul Nicholas Leech, of the Chemical Laboratory of the American Medical Association, page 288 of this issue.
>
> "On the other hand, the excess profit fully warrants the extensive and shrewdly-worded advertising campaign now in progress, a campaign which must eventually fail, because in the first place, it is contrary to the prevailing spirit of modern advertising, the motive of which is constructive rather than destructive, and, in the second place, it appeals merely to the temporary ignorance of the public at large, and has no basis in fact.
>
> "We have been informed that the Custodian of Alien Enemy Property has taken charge of the stock interests of alien enemies in the company conducting this propaganda. Surely the Custodian will not care, even in a trustee capacity, to continue as a participant in a misleading campaign whose sole purpose is the perpetuation of a monopoly hitherto enjoyed under full patent protection."

The article to which the editorial refers is a somewhat technical one giving the findings of an examination made, at the request of the Council on Pharmacy and Chemistry, in the Chemical Laboratory of the American Medical Association by Paul Nicholas Leech, Ph.D., of various American brands of acetylsalicylic acid (aspirin). The result of the investigation amy be summed up briefly in the statement that there are on the American market, made by American firms, several brands of acetylsalicylic acid that are just as good as, if not better, than the Bayer product.

THE JOURNAL has called attention to the misleading propaganda on the part of the Bayer Company (Farbenfabriken vorm. Friedr. Bayer & Co.), in its attempt to perpetuate the monopoly granted under our inequitable patent laws. This is done by conveying the inference that the only pure acetylsalicylic acid on the market is that known as "Aspirin-Bayer." Physicians should again be reminded of the facts in the case of aspirin: Practically no other country in the world, and certainly not Germany, the original home of aspirin, would grant a patent either on acetylsalicylic acid, itself, or the process for making it. The United States granted both! As a result no one in this country except the Bayer Company could for seventeen years manufacture or sell acetylsalicylic acid either under its chemical name or under any other name. Nor was it permissible for hospitals or individuals to import it. While the monopoly held, the American people were compelled to pay from six to ten times as much for acetylsalicylic acid as were the people of Great Britain, France, Germany, Austria-Hungary, Denmark, Holland, Norway or Sweden. At a time when American druggists were compelled to pay 43 cents an ounce for acetylsalicylic acid as aspirin, just across the border in Canada it sold for about one-third the price.

About a year ago the Council on Pharmacy and Chemistry announced that "Aspirin-Bayer" had been deleted from New and Nonofficial Remedies while the scientific term, acetylsalicylic acid, was retained along with standards to insure its quality. The necessity for a standard becomes evident when it is remembered that acetylsalicylic acid is not yet an official drug, and its purity, therefore, is not subject to the control of the federal Food and Drugs Act. It is worth while at this time to remind physicians that several brands of acetylsalicylic acid (aspirin) have been found to comply with the standards set by the Council on Pharmacy and Chemistry and have been admitted to New and Nonofficial Remedies. These, of course, are thereby subject to the control of the federal law to conform to the standard to which they profess.

Leech's report gives still greater weight to the suggestion that has been made for some time, viz., that physicians should prescribe acetylsalicylic acid under its scientific name rather than its proprietary name, even though, in the opinion of THE JOURNAL, the proprietary name, aspirin, has become common property since the expiration of the acetylsalicylic acid patent. Every consideration of public interest, of patriotism and of ordinary common sense should prompt physicians to specify acetylsalicylic acid in writing prescriptions. —[*Reprinted from J. A. M. A., April 13, 1918, p. 1097.*]

DR. A. W. CHASE'S NERVE PILLS

A. H. Clark, Ph.G., B.S.

(*Reprinted, with additions, from J. A. M. A., Sept. 7, 1918 p. 844*)

The label on the box of "Dr. A. W. Chase's Nerve Pills" states that they are "prepared for the Dr. A. W. Chase Medicine Co., Props., Buffalo, N. Y.," and that they are "used in the treatment" of "thin and watery blood, nervous disorders, brain fag, nervous headache, nervous dyspepsia, irregular heart action, sleeplessness," etc. A circular within the box sets forth the alleged virtues of these pills and of other products of the company. This circular calls attention to the use of these pills in the treatment of almost everything from pale, sallow complexion, to paralysis and locomotor ataxia. Sexual debility and female troubles occupy a prominent place among the diseases and symptoms which are made "next to impossible of occurrence" through the use of these pills.

The circular declares that on every box of these pills will be found a portrait of Dr. A. W. Chase, of Chase's Family Recipe Book fame. The inference is that these pills are made according to a formula in this book. A careful search of Chase's Receipts, or Information for Everybody,[1] also a later edition[2] failed to reveal a formula for any such pills as the ones purchased. On page 130 of the 1900 edition a formula is given for "Nervous Pills." These are essentially an alcoholic extract of Ignitia amara (St. Ignatius bean). These were said to be originated in 1854 by Rev. John W. Dagnal, the "Retired Physician," and much used by Professor Palmer of the University of Michigan. Dr. Repheto[3] calls attention to these in answer to an inquiry about Chase's pills. He states that this formula was much used by eclectics and because of poor results Dr. John King of Cincinnati introduced a substitute composed of extract of gentian, powdered savine leaves, powdered Ignatius leaves, and iron iodid.

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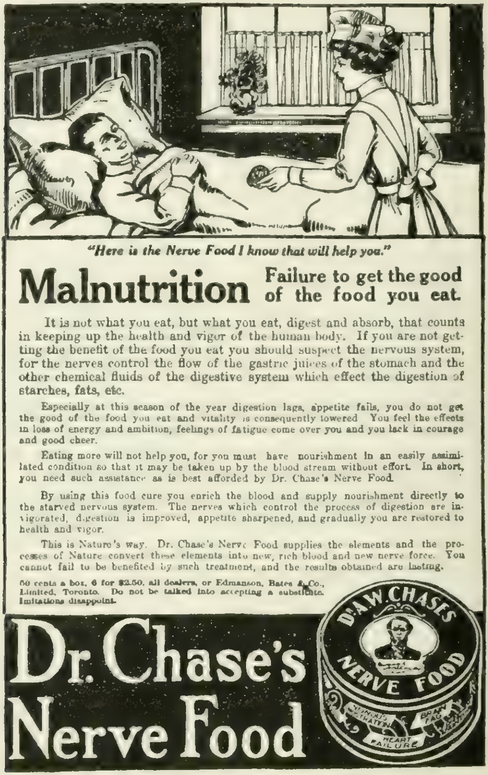
[1] By A. W. Chase, M.D., Published by R. A. Beal, Ann Arbor, Mich., 1900.

[2] Dr. Chase's Combination Receipt Book, F. B. Dickerson Co., Detroit, 1915.

[3] Medical World, Aug. 1912, p. 336.



"Here is the Nerve Food I know that will help you."

Malnutrition **Failure to get the good of the food you eat.**

It is not what you eat, but what you eat, digest and absorb, that counts in keeping up the health and vigor of the human body. If you are not getting the benefit of the food you eat you should suspect the nervous system, for the nerves control the flow of the gastric juices of the stomach and the other chemical fluids of the digestive system which effect the digestion of starches, fats, etc.

Especially at this season of the year digestion lags, appetite fails, you do not get the good of the food you eat and vitality is consequently lowered You feel the effects in loss of energy and ambition, feelings of fatigue come over you and you lack in courage and good cheer.

Eating more will not help you, for you must have nourishment in an easily assimilated condition so that it may be taken up by the blood stream without effort. In short, you need such assistance as is best afforded by Dr. Chase's Nerve Food.

By using this food cure you enrich the blood and supply nourishment directly to the starved nervous system. The nerves which control the process of digestion are invigorated, digestion is improved, appetite sharpened, and gradually you are restored to health and vigor.

This is Nature's way. Dr. Chase's Nerve Food supplies the elements and the processes of Nature convert these elements into new, rich blood and new nerve force. You cannot fail to be benefited by such treatment, and the results obtained are lasting.

60 cents a box, 6 for $2.50, all dealers, or Edmanson, Bates & Co., Limited, Toronto. Do not be talked into accepting a substitute. Imitations disappoint.

Dr. Chase's Nerve Food

"Dr. A. W. Chase's Nerve Pills" used to be called "Dr. Chase's Nerve Food" before the Federal Food and Drugs Act made falsifying expensive. Then "Food" became "Tablets" and, later, "Pills." In Canada, however, it continued to be sold as a "Food." The illustration above is a reduced photographic reproduction of an advertisement in a Canadian magazine.

The examination made in the chemical laboratory, discussed below, shows that "Dr. A. W. Chase's Nerve Pills" do not correspond in composition to pills prepared by either of the formulas mentioned above. They are coated, chocolate colored, and have a strongly persistent bitter aloes-like taste. The coating readily washed from the pills but the pill mass did not readily disintegrate. Even standing over night in water they were not entirely disintegrated.

The pills weigh approximately 0.318 gm. (5 grains) with coating; the medicament alone weighs 0.210 gm. (3.5 grains). Microscopic examination did not show vegetable structure. Qualitative examination showed the absence of chlorids, bromids, iodids, phosphorus and phosphorus compounds. Abundance of sulphate was present, also carbonate. Iron and manganese were present in large quantities, calcium and sodium in lesser amounts, aluminum and magnesium in small amounts. The manganese was probably present as black oxid (manganese dioxid), since the manganese did not dissolve in water, and the pills with hydrochloric acid gave abundance of chlorin. Emodin bearing drugs were present and alkaloids also were present in small amounts. Iron, manganese, and sulphate were determined quantitatively. The iron oxid weighed indicated the presence of iron equivalent to 0.0395 gm. (⅔ grain) anhydrous ferrous sulphate in each pill. The amount of manganese pyrophosphate obtained indicated manganese equivalent to 0.021 gm. (⅓ grain), manganese dioxid in each pill. The quantity of alkaloid present was so small that it could not be determined accurately.

The chemical examination indicates that these pills contain iron, possibly in the form of ferrous sulphate which is in a state of more or less decomposition due to exposure and contact with the other constituents of the pills, manganese dioxid, aloes or aloin, vegetable extractive, and traces only of some alkaloidal drug.

Analytical Details

Dr. A. W. Chase's Nerve Pills were oval, coated, chocolate-colored. The medicament was very dark colored and had an intensely bitter, aloes-like taste. Twenty-five pills weighed 7.95 gm., or 0.318 gm. per pill, which is approximately 5 grains. Deprived of coating, ten pills weighed 2.1082 gm., or approximately 3.5 grains.

Microscopic examination did not show vegetable structure.

QUALITATIVE EXAMINATION

Phosphorus.—Five pills were examined by Mitscherlich's method (Autenreith-Warren: The Detection of Poisons and Powerful Drugs, p. 5). None could be detected.

Phosphorus Compounds.—Two pills were repeatedly evaporated with nitric acid until all organic matter was destroyed. A solution of the residue in nitric acid gave no precipitate with ammonium molybdate test solution.

Chlorid, Bromid, Iodid.—Aqueous extract, or extract in dilute nitric acid failed to give a precipitate with silver nitrate. When warmed with hydrochloric acid, or concentrated nitric acid, no vapors of bromin or iodin were noticed.

Sulphate.—The solution prepared for the detection of phosphorus compounds gave an abundant precipitate with barium chlorid solution.

Carbonate.—Some effervescence took place with dilute acids. The gas formed was odorless and colorless. An aqueous extract of the pills was neutral to litmus, therefore the carbonate was not sodium or potassium.

Iron.—An aqueous extract with potassium ferrocyanid gave some blue precipitate. With potassium ferricyanid no blue precipitate was produced. Extracted with slightly acidulated water the acid solution gave an abundant precipitate with potassium ferrocyanid and some coloration only with potassium ferricyanid. The iron present is not in a form very soluble in water and is practically all in the ferric state.

Manganese Dioxid.—The pills contained a black granular substance which was not readily soluble in dilute acids. After dissolving all the iron with dilute sulphuric acid, and by means of careful decantation after shaking with water, some of this black powder was obtained practically free from other material in the pills. When warmed with fairly strong hydrochloric acid it dissolved with the evolution of chlorin. In this solution manganese was detected by the usual methods.

Calcium, Sodium.—Traces of these metals were found by the usual methods.

Emodin.—Three pills were extracted with water, the aqueous solution made slightly acid and shaken with benzol. The benzol solution shaken with ammonia gave a distinct red color.

Aloes or Aloin.—An aqueous extract heated with borax became green.

Alkaloids.—Ten pills thoroughly powdered and examined by the method given under Sulpherb Tablets gave reactions for alkaloids with iodin, Meyers', and tannic acid solutions. The quantity of alkaloid was so small that it could not be titrated.

QUANTITATIVE EXAMINATION

Iron.—Ten pills weighing 2.1224 gm. without the coating were ignited to destroy organic matter. The residue was dissolved in hydrochloric acid and the solution divided into two equal parts. The iron was determined gravimetrically as Fe_2O_3 in the usual way. One part gave 0.115 gm. Fe_2O_3, the other part, 0.1167 gm., or 0.2317 gm., for the ten pills. This was found to contain 0.0167 gm. silica, leaving 0.215 gm. Fe_2O_3 from the ten pills. This calculated to anhydrous ferrous sulphate is equivalent to 0.4125 gm., or 0.0413 gm. in each pill, or 19.43 per cent.

Sulphate.—Ten pills weighing 2.1082 gm. without coating were evaporated repeatedly with a mixture of hydrochloric and nitric acids until all organic matter was destroyed. The solution was filtered and made up to 50 c.c. In 50 c.c. of this solution (representing one pill) the sulphate was determined as $BaSO_4$ in the usual manner. One determination gave 0.0607 gm., another 0.0607 gm. $BaSO_4$. This is equivalent to 0.0395 gm. anhydrous ferrous sulphate in one pill or 18.74 per cent.

Manganese.—Manganese was determined in the filtrate from the iron determinations above, according to the method of Gibb's (Scott: Standard Methods of Chemical Analyses, 1917, p. 262). One experiment gave 0.1756 gm. $Mn_2P_2O_7$, another 0.1738, or an average of 0.1747 from five pills. This is equivalent to 0.1057 gm. MnO_2, or 9.96 per cent, or 0.0211 gm. per pill.

B. IODINE AND B. OLEUM IODINE

A. H. Clark, Ph.G., B.S.

(*Reprinted from J. A. M. A., Feb. 1, 1919, p. 365*)

"B. Iodine" products are marketed by the B. Iodine Chemical Company, Cincinnati, Ohio; John Bohlander, A M., M.D., is said to be the discoverer. They consist of "B. Iodine," "B. Oleum Iodine," and "B. Aqua Iodine." B. Iodine and B. Oleum Iodine were submitted to the Council.

In a circular submitted by the B. Iodine Chemical Company, B. Iodine is said to be "Nitrogen Hydrate of Iodin." It is claimed that "coming in contact with water, H_2O a chemical change takes place forming Hydro Oxid of Iodin, the Nitrogen of the Nitrogen Hydrate of Iodin escaping, the balance taking up one of oxygen of the water. Its companion, the H_2, escaping at the same time with the Nitrogen then combining with the remainder of the water to form the solution of Hydrogen Oxid of Iodin; so you can readily see that you really have a pure water of Iodin, nothing but the H, the O and the I."

Specimens of B. Iodine and B. Oleum Iodine (B. Iodine Chemical Company) and an advertising pamphlet were sent to the Council by John Bohlander, A.M., M.D., with the declaration:

> "Well knowing the value of Iodin in surgical operations and dressings, prompted me for the benefit of my fellow physicians as well as myself, and for Humanity's sake, to make Iodin my master-piece in chemistry.
>
> "After several years of diligent work in my private laboratory I succeeded in discovering a new product of Iodin—Nitrogen, hydrate of Iodin."

B. IODINE

According to the circular, B. Iodine is soluble in alcohol, chloroform, and ether. Also it:

> "Has odor, taste, melting and boiling point, same as regular Iodin, has a great affinity for water and will respond to all the tests of Iodin. Appears in a Bluish Black Granulated mass or powder. When heated in vaporating dish will throw off large purple volumes of Iodin leaving a slight white crystaline precipitate, which on continuous heating will entirely disappear. With careful manipulation you can get prismatic needle point like crystals, looking like spores of glass, these dissolving in water will yield pure Iodin coloring the water Iodin.
>
> "PHARMACOLOGIC, THERAPEUTICAL AND PHYSIOLOGICAL ACTION: Same as Iodin, being of a colloidal nature has the advantage of being more readily absorbed and taken up by all cellular structure, thus getting a perfect cellular medication of Iodin."

A sample of B. Iodine, marked "Nitrogen Hydrate of Iodin" was submitted by the manufacturers and this sample was examined.

B. Iodine was found to be a granular powder, almost black with a purple cast. It has an odor of iodin and dissolves in water readily. It is also quite soluble in alcohol, but not entirely soluble in chloroform and ether. Ether quickly dissolves iodin from B. Iodine leaving a residue of a white granular substance. Chloroform acts the same as ether except that the iodin is dissolved out with some difficulty. On heating B. Iodine, vapors of iodin escape. If the heating is done on a water bath, a residue of a white granular substance, subsequently identified as ammonium iodid, remains. If heated in a bunsen flame, no residue remains. These tests all indicate that iodin is held in the form of a simple mixture.

Ammonia: B. Iodine when mixed with an excess of sodium hydroxid and warmed, evolves ammonia.

Iodine: 0.1567 gm. B. Iodine dissolved in water required 5.88 c.c. tenth-normal sodium thiosulphate solution indicating 48.28 per cent. iodin. 0.3721 gm. B. Iodine required 14.18 c.c. tenth-normal sodium thiosulphate solution indicating 48.37 per cent. iodin. The average is 48.33 per cent. iodin.

Ammonium Iodide: 0.3453 gm. of the residue after heating B. Iodine on a water bath until all iodin had volatilized was dissolved in water, acidulated with phosphoric acid, and hydrogen dioxid solution added. The liberated iodin was extracted with chloroform and titrated with tenth-normal sodium thiosulphate. 23.78 c.c. were required indicating 0.3447 gm., or 99.83 per cent., ammonium iodid.

A mixture of 5 gm. iodin and 5 gm. ammonium iodid has the properties of B. Iodine mentioned above.

The conclusion is that B. Iodine is essentially a mixture of iodin and ammonium iodid in equal parts, the two substances being finely powdered and intimately mixed.

B. OLEUM IODINE

The following regarding B. Oleum Iodine is quoted from the circular submitted:

> "B. OLEUM IODINE: Iodine soluble in mineral oil 5 and 10% for Nasel, Pharyngeal, Laryngeal, Bronchial, Rectal, etc., and all meucoid affections and abnormal conditions of the mucous membrane."

A sample of B. Oleum Iodine was submitted by the manufacturer and examined. The label on the bottle states that it is 5 per cent. B. Oleum Iodine in mineral oil. This sample has the characteristics of a solution of iodin in liquid petrolatum. It is oily and has the characteristic violet color.

Ammonia: B. Oleum Iodine, since it is presumed to be a solution of B. Iodine, was examined for ammonium compounds. A small quantity was mixed with an equal volume of strong sodium hydroxid solution and heated. No ammonia was evolved. A few crystals of ammonium chlorid were added to a little of B. Oleum Iodine and treated as above. Ammonia was readily detected.

Iodine: 5.255 gm. B. Oleum Iodine was dissolved in chloroform and placed in a separator. A solution of potassium iodid was added and the iodin titrated with tenth-normal sodium thiosulphate solution. It required 3.5 c.c. indicating 0.85 per cent. iodin.

The conclusion is that B. Oleum Iodine is a simple solution of iodin in liquid petrolatum to the extent of 0.85 per cent. and not 5 per cent. as claimed. Furthermore, it is not a solution of B. Iodine since no ammonium compound is present.

The preceding report was submitted to the Council on Pharmacy and Chemistry by the referee in charge of Iodin preparations.

The Council adopted the report and declared B. Oleum Iodine inadmissible to New and Nonofficial Remedies because:

1. The composition is incorrectly declared. B. Iodine is not a newly discovered iodin compound, "Nitrogen Hydrate of Iodine," but a mixture of iodin and ammonium iodid. B. Oleum Iodine is not a 5 per cent. solution of B. Iodine as suggested by the statement on the label and in the advertising, but a solution of iodin in liquid petrolatum containing about 0.85 per cent. of iodin.

2. Since B. Iodine is a mixture of iodin and ammonium iodid, its solution in water will have the properties of other solutions of iodin made by the aid of iodid, such as a dilution of tincture of iodin or of compound solution of iodin (Lugol's solution). Hence, the therapeutic claim that B. Iodine "being of a colloidial nature has the advantage of being more readily absorbed and taken up by all cellular structure, thus getting a perfect cellular medication of Iodine," is unwarranted.

3. The names "B. Iodine" and "B. Oleum Iodine" are not descriptive of the pharmaceutical mixtures to which they are applied.

4. B. Iodine and B. Oleum Iodine are unessential modifications of established articles. B. Iodine has no advantage over tincture of iodin or compound solution of iodin. (As more convenient of transportation, the Medical Department of the U. S. Army supplies its field hospitals with a mixture of iodin and iodid ready for solution in water, either in tablet form or in powdered form in tubes.) Solutions of iodin in liquid petrolatum may be readily prepared (Reports Council Pharm. and Chem., 1917, p. 148).

The Laboratory's findings and the Council's conclusions were sent to the B. Iodine Chemical Company. The following reply was received:

> Your letter of the 21st inst., received and contents noted and cannot quite agree with your report.
>
> Reasons why: NH_4I, a Nitro Hydrate Iodide; NH_4I_2, a Nitro Hydrate Iodate; and $NH_4I_2I_2$, Per Iodide, a molecular compound, which I claim, they all being of a NH group, so what can be the objection of Nitrogen

Hydrate of Iodine? Of course when your chemist, with the aid of heat, drove off all the Iodine, he naturally brought it back to a NH_4I. There's where he gets the A.M. I claim a molecular compound.

The Oil of Iodine I sent you by mistake was a 1 per cent. and not a 5 per cent. as marked. I claim it is made from the resublimed Iodine in mineral oil and not the B. Iodine. I claim a 5 per cent has heretofore never been accomplished, so I therefore can claim something new.

Tr. Iodine contains Alcohol and Potash as a base, the alcohol a dehydrater and Potash an escharotic, and all other soluble Iodines like the tincture have a metallic base. Mine has not. My iodine is compatable almost with all the salts, alkaloids, tannates, and even the metals. You can't say that for the tincture or the others. Now why should mine not be superior to others?

Preparations as yet are not on the market and a few pamphlets were printed to meet with the requirements of your rulings and approval and shall be corrected if we only can agree on a proper name as you may suggest.

Yours very truly,

THE B. IODINE CHEMICAL CO.
By John Bohlander, A.M., M.D.

P. S. We are sending you under separate cover another sample of the Oil of Iodine which is a 5 per cent. solution, and allowing for deterioration will test at least four per cent.

The referee in charge of the preparations submitted the above letter to the Council with the following comments:

The principal statements in the letter are essentially erroneous or misleading: Mixtures or double salts of ammonium iodid and iodin were not discovered by Dr. Bohlander, and are nothing new. Watery solutions of iodin by means of an iodid have long been known and used in the form of Lugol's solution.

There is no evidence that ammonium iodid is less irritating than potassium iodid. On the contrary, ammonium salts are generally more irritating than the corresponding potassium salts. B. Iodine is not compatible with alkaloids, but behaves essentially like Lugol's solution. The A. M. A. Chemical Laboratory reports that the new sample of B. Oleum Iodine contains only 1.2 per cent. of free iodin, instead of the claimed 5 per cent. It is therefore somewhat weaker than the solution of iodin in petrolatum prepared by the A. M. A. Chemical Laboratory (Reports Council Pharm. and Chem., 1917, p. 148; Annual Report of the A. M. A. Chemical Laboratory, 1917, p. 88).

However good Dr. Bohlander's intentions may be, the statements that he makes about his products are misleading or erroneous, and the products are ineligible for N. N. R.

PART II

REPORTS ABSTRACTED AND REPRINTED FROM THE JOURNAL A. M. A., AND FROM THE REPORTS OF THE COUNCIL ON PHARMACY AND CHEMISTRY

GUAIODINE

(Reprinted, in part, with additions, from the J. A. M. A., April 16, 1918, p. 1026)

Guaiodine is manufactured by the Intravenous Products Co., Denver, Colorado. The "literature" which accompanies the product describes Guaiodine as "an electro-chemically prepared iodine, suspended in oil, containing iodine, the same strength as the U. S. P., tincture of iodine, or 7 per cent., together with a therapeutic dose of guaiacol." The Intravenous products Co. claims that Guaiodine is made by an "electro-chemical process of preparing colloidal iodine," discovered by one E. B. Page, and that by this process the tendency of iodin to produce iodism has been "overcome." It is said to be "pre-eminently an antiseptic and germicide."

At the request of the Council on Pharmacy and Chemistry, the Chemical Laboratory of the American Medical Association examined Guaiodine.

Guaiodine is a dark brown oily liquid with a specific gravity of 0.9845 at 15.6° and an odor suggestive of guaiacol.. Its solubilities were those of a fat. Free iodin was absent in a recently purchased specimen but small amounts were present in an older one. Steam distillation indicated that the product consisted of volatile and nonvolatile constituents. The volatile matter was concluded to consist, in the main, of guaiacol or some guaiacol-like body, and the nonvolatile matter to be an iodized fatty oil. Quantitative determinations indicated that Guaiodine contained about 7.25 per cent. of iodin in combination, and that it is composed approximately of 3 per cent. volatile matter and 97 per cent. nonvolatile matter. Hence, Guaiodine appears to be an iodized fatty oil to which a small amount of guaiacol or some guaiacol-like substance has been added.

In reporting the Laboratory's investigation to the Council on Pharmacy and Chemistry, the referee in charge of Guaiodine declared that the implied claims that its antiseptic action corresponds to that of free iodin, were false and the therapeutic recommendations made for the preparation unwarranted.

On the recommendation of the referee, the Council voted that Guaiodine be declared inadmissible to New and Nonofficial Remedies because of false statements as to composition and action.

Details of Analysis

Total Iodin.—(Kendall's Method, J. Am. Chem. Soc., 1912, p. 894):

(*a*) 0.7152 gm. on fusion with alkali, oxidation of the iodid to iodate by means of sodium hypochlorite, liberation of the iodin by addition of iodid and subsequent titration of the iodin with tenth-normal sodium thiosulphate (factor 0.9505) required 25.7 c.c. of thiosulphate solution equivalent to 0.0516 gm. iodin or 7.21 per cent.

(*b*) 0.8500 gm. required 29.3 c.c. of sodium thiosulphate solution, equivalent to 0.0619 gm. of iodin or 7.28 per cent.

Free Iodin.—A chloroformic solution of the product was shaken repeatedly with portions of a 10 per cent. solution of potassium iodid. On the addition of starch paste to the latter no blue color developed.

Traces (less than 0.1 per cent.) of free iodin were found to be present in a specimen of Guaiodine purchased in 1916.

Iodid.—A chloroform solution of the product was shaken with water. The aqueous layer was then separated, acidified, ferric chlorid solution added, and shaken with chloroform. The chloroformic layer turned slightly pink.

On shaking 5 c.c. of Guaiodine with 25 c.c. of distilled water in separatory funnel allowing to stand for a period of twenty-four hours and separation of the aqueous layer, the last reacted positively for iodid with silver nitrate solution after acidification with nitric acid. After continued treatment with fresh portions of distilled water for four consecutive days, similar results were obtained, indicating that the presence of iodid was apparently due to the hydrolysis of the product.

Iodate.—Violet vapors were obtained by (a) heat, (b) heat and sulphuric acid.

A chloroformic solution of the product was shaken with water and the latter separated. On acidification, addition of potassium iodid and starch no blue color developed.

Reaction toward Litmus.—Chloroformic solution and aqueous extract of chloroformic solution were neutral to litmus.

Steam Distillation.—Fifteen c.c. of the product were distilled in the usual manner. The volatile matter passed over with the distillate but no separation of oil occurred.

(*a*) *Volatile Constituent.*—The distillate was a clear liquid with a strong odor of guaiacol. Guaiacol was tested for by the following method (Commercial Organic Analysis, Allen, Ed. 3, **2**: Part 2, p. 243):

The distillate was shaken out with chloroform. Solid potassium hydroxid was added to a portion of the chloroformic solution and heated on a steam bath. A red-purple coloration was produced, indicating the presence of guaiacol.

(*b*) *Nonvolatile Constituent* (*Residue*).—The residue in the steam flask consisted of a dark brown viscous oil with a bland fatty odor. It was found to be completely saponifiable by an alcoholic solution of potassium hydroxid, indicating that it consisted of a fatty oil. The saponified portion readily gave a test for iodin, showing that the nonvolatile portion was an iodized fatty oil.

(*c*) The amount of volatile matter present in the compound was determined in the following manner:

6.341 gm. of the product were weighed into a shallow beaker and placed on a water bath. It was frequently rotated and weighed from time to time. When it came to a constant weight it was found to have lost 0.1865 gm. or 2.94 per cent. Thus the product was found to consist of 97.06 per cent. of an iodized fatty oil and 2.94 per cent. of a volatile constituent, which from its odor, solubility in water and chemical behavior appears to be guaiacol or some guaiacol-like substance.

The manufacturer's statement that the product contains "iodin suspended in oil" gives the impression that the product contains suspended iodin *in the elementary state.* If such were the case, the product should respond to tests for free iodin. Furthermore, it is a well-known fact that when iodin is added to a fatty oil an iodin addition product is formed, that is, a chemical combination takes place, resulting in the formation of a definite chemical compound. The iodin in the resulting compound cannot be considered to be in a state of suspension, nor can it be considered as existing in the elementary state.

SYPHILODOL

(Reprinted, with additions, from J. A. M. A., May 18, 1918, p. 1450)

The shortage of arsphenamin (salvarsan) has made the sale of substitutes a profitable business. In many of these substitutes the earmarks of dishonesty have been obvious, so that detection of their falsity was relatively simple. In the case of "Syphilodol" marketed by the French Medicinal Company, Inc., New York, the deception has been practiced more skilfully. In the circular announcing their preparations, we read:

> "It seems fitting at this time, when the American physicians are doing so much for France, that there should be a reciprocation in some way.
>
> "Attempting to enhance somewhat this mutual interchange, we are presenting some of those scientific products, which have been so successfully used in France,——"
>
> "The effect of SYPHILODOL is very similar to salvarsan and neosalvarsan, but it has the advantage of being more lasting in its results and more pleasing in the manner of its preparations, in that it is put up in the form of tablets, and, also, in hermetically closed glass syringes or ampules, so that it may be administered either by the mouth, intravenously or intramuscularly, at the discretion of the physician. Patients averse to the use of the hypodermic needle may be treated expeditiously by the use of the tablet form of the medicine."

In addition to Syphilodol, the French Medicinal Co. also sell "Vichy Fruti," a combination of salts, "Urodol," an "alkaline salt of the famous European Springs which is noted for breaking up and dissolving uric acid rapidly" and "Syloiodol," "French Preventive" which is described as "a solution of iodol incorporated into bougie."

"Syphilodol," we are told, is "a synthetic chemical product of *silver, arsenic* and *antimony,* scientifically prepared after the formula of the *late* Dr. Alfred Fournier of paris." (Italics ours.—Ed.). It is also claimed that "Prof. Metchnikoff and other noted French Scientists have made exhaustive tests of syphilodol and found it superior to the other products, in the treatment of syphilis." In the advertisements, Fournier and Metschnikoff are the only names given of alleged endorsers; both of these men are dead and cannot protest. True, Fournier did considerable work on a legitimate synthetic of antimony, silver and arsenic having a general chemical constitution similar to arspenamin, but so far as we are aware, there has been no publication by these men on "Syphilodol." It would seem that the valuable work and high reputation of Fournier and Metchnikoff are being capitalized by the French Medicinal Company in their endeavor to foist a nostrum on the medical profession of this country.

"Syphilodol" comes in two forms—ampules and tablets. An order for two 0.4 ampules brought an elaborate case, much like those used to hold the popular style safety razors. The ampule itself was a "classy" affair evidently made by a glass expert; the hypodermic needle was enclosed in a novel sealed glass device. The price of each ampule is $3. No such fancy garnishments came with the tablets, although they are listed at $4.50 for twenty-five—18 cents a tablet! In the "Syphilodol" advertising it is emphasized that both the tablets and ampules are to be administered. For example:

> "Syphilodol is dispensed in the form of tablets and also in hermetically closed glass syringes or ampules so that it may be used either by the mouth, intravenously or intramuscularly at the discretion of the physician. An advantage of the tablets is that they can and should be given during the interim between the injections."

LABORATORY REPORT ON SYPHILODOL

Several samples of "Syphilodol" were sent to the American Medical Association Chemical Laboratory by readers of The Journal. An original bottle of tablets was ordered direct from the French Medicinal Company. The bottle contained 25 yellow tablets, having an average weight of 0.276 gm. (4¼ grains). After being powdered, "Syphilodol" was found to be only partially soluble in water (the excipient is soluble) and to be neutral in reaction. These findings contradict the claims on the circular accompanying the bottle to the effect that "Syphilodol is a yellow powder, soluble in water, and has an acid reaction." Qualitative tests indicated the presence of mercury, sucrose (cane sugar), iodid, calcium, sulphate, fatty material, a trace of silver, a trace of arsenic and a very minute trace of antimony; a red dye was also present. Both qualitative and quantitative data showed that the mercury was present in the form of mercurous iodid (yellow iodid of mercury—hydrargyri iodidum flavum). Quantitative estimations yielded the following:

Silver (Ag^+)	0.001	per cent.
Mercury (Hg^+)	11.1	per cent.
Iodid (I^-)	7.8	per cent.
Sucrose (Cane sugar)	72.0	per cent.
Ash (Calcium Sulphate)	2.5	per cent.
Ether-soluble material (Fatty material—Petrolatum)	3.5	per cent.

Thus each tablet of "Syphilodol" contains approximately ¾ grain of mercurous iodid. An ampule of "Syphilodol," labeled 0.4 gram, contained approximately 1.5 c.c. of a liquid which after evaporation on a water-bath left a residue weighing 0.8 mg., or 1/80 grain. A second ampule held about 2 c.c. of liquid, which contained a trace of arsenic (less than 0.00001 gm., or 1/6000 grain); a very small amount of mercury was indicated but not definitely established. The liquid had the physical characteristics of water.

Accompanying "Syphilodol" advertising sent to physicians is a circular letter inviting the doctor to become a member in the "United States Bacteriological and Research Institute." The "institute" seems to be a means of suggesting that the physician have bacteriologic, pathologic and serologic examinations made on behalf of his patients. In view of the fact that it is to the commercial interest of the French Medicinal Company to have as many users of "Syphilodol" as possible, it would be interesting to know what proportion of the Wassermann tests are reported negative.

Shorn of its mystery, Syphilodol the "synthetic chemical product of silver, arsenic and antimony" is essentially mercurous iodid—yellow iodid of mercury.

Details of Analysis

SYPHILODOL TABLETS

In France there has been on the market for some time a synthetic compound of silver, arsenic and antimony having the general structure of arsphenamin. Structurally, the formula as given by Bonard, Danyss and Tournier is $(C_{12}H_{12}N_2As_2)$ $2AgBrSbO$ $(H_2SO_4)_2$—dioxy=diamino arsenobensolstibicosilver sulphate. As the advertising matter for "Syphilodol" referred to the synthetic compound of silver, antimony and arsenic, and also to its use in syphilis by Fournier, the above compound was first suspected. However, the general characteristics of syphilodol tablets, such as partial solubility in water, but not soluble in sodium hydroxid, sodium bicarbonate or acids, threw doubt on the hypothesis. When a small amount of the powdered tablets was treated with water, a yellow residue could be filtered off; the filtrate was pink, opalescent, which on standing gave a clear pink solution, and a small yellow precipitate. The residue, when allowed to remain in sulphuric acid solution (20 per cent.) over night became red; on boiling, the red precipitate with sulphuric acid, the precipitate volatilized and could be condensed in a watch glass. Adding a pinch of manganese dioxid to the hot sulphuric acid mixture caused an evolution of iodin fumes. A small amount of powdered syphilodol tablets was placed in the sunlight; they turned from yellow to black. All these reactions are typical of mercurous iodid—yellow iodid of mercury.

MERCURY, SILVER, ARSENIC, ANTIMONY

I. *Mercury.*—Two methods were used to determine the mercury: (*a*) 1.4535 gm. of powdered "syphilodol" was treated with 10 c.c. of a 50 per cent. sodium sulphid solution. The solution was then transferred with washings (about 20 c.c.) to a cathode cup, previously weighed with its contained mercury. The mercury compound was electrolyzed by a current of about 8 volts and 3 amperes, using a rotating anode. The solution (and some sulphur suspension) was removed by siphon, pouring in water until the amperage of the current was close to zero (U. S. P., IX, p. 587). The increased weight in mercury was 0.1612 gm.

II. To serve as a check on the foregoing method, mercury was also determined in the following method, which also allowed systematic tests for silver, antimony and arsenic. (*b*) 1.1023 gm. of the sample was placed in an Erlenmyer flask, 50 c.c. of water, 50 c.c. of sodium hydroxid solution (10 per cent.) and 20 c.c. of formaldehyd solution, U. S. P., added. The solution was boiled for ten minutes and maintained at temperature of steam bath for two hours. (This reduces the mercury salt to mercury and any silver salt to silver; antimony would probably be likewise reduced.) The precipitated mercury was transferred by water, and concentrated nitric acid added. (The nitric acid solution is boiled to oxidize all mercurous nitrate to mercuric nitrate.) A small white precipitate was obtained at this point which seeemd to be insoluble in aqua regia (calcium sulphate). The filtrate from this precipitate, which was washed well, was tested with one or two drops of dilute hydrochloric acid and a faint precipitate formed; this was filtered off through extra fine filter paper and washed repeatedly. The paper and precipitate was heated with potassium cyanid solution over night, filtered and the filtrate electrolyzed in a platinum dish. The increase in weight of the dish was 0.00018 gm., or 0.001 per cent. Into the platinum dish some nitric acid was poured, then diluted, and a drop of hydrochloric acid added. A turbidity was produced which cleared on the addition of excess of ammonium hydroxid solution (*silver*). The filtrate from the nitric acid treatment was electrolyzed, this time in a platinum dish, and the liquid carefully removed, washed carefully with redistilled alcohol and ether. The mercury, which could be seen easily by the naked eye, weighed 0.1200 gm., equivalent to 10.89 per cent. of mercury.

III. *Arsenic and Antimony.*—About 3 gm. of the powdered specimen was digested with sulphuric acid in a Kjeldahl flask. One-half portion (which was evaporated almost to dryness and treated with 5 c.c. of concentrated hydrochloric acid) was submitted to treatment with hydrogen sulphid, diluted, and saturated with hydrogen sulphid. The precipitate was treated in the usual manner of the group separation with warm ammonium sulphid solution. The filtrate from this treatment was acidulated with hydrochloric acid, the precipitate removed, and treated with concentrated hydrochloric acid. The substance insoluble in hydrochloric acid was treated with more concentrated hydrochloric acid and a crystal of potassium chlorate. The solution was tested after the Gutzeit method of the Pharmacopeia IX, for *arsenic*. A very small amount was indicated. The hydrogen sulphid test was not indicative. The solution which might contain the *antimony* was tested with hydrogen sulphid. In one case only was a slight orange coloration produced. No antimony was deposited on platinum foil in the presence of granulated zinc. These tests were run in triplicate.

Iodid.—Iodid was determined by the Carius method (*a*) 0.7412 gm. yielded 0.1112 gm. silver iodid, equivalent to 8.09 per cent.; (*b*) 0.5319 gm. yielded 0.0751 gm., equivalent to 7.80 per cent. The iodid and mercury were in proportions comparable to mercurous iodid.

Ash.—(*a*) 0.9159 gm. when ignited to constant weight yielded 0.0232 gm., equivalent to 2.52 per cent. ash; (*b*) 1.3008 gm. treated with water and the residue filtered on a Gooch filter and ignited. The ash of the residue was 2.51 per cent. (the mercurous iodid volatilized). The ash was calcium sulphate.

Sucrose.—1.3008 gm. of the sample was treated with water and filtered by suction through a Gooch crucible. The filtrate and washing were carefully transferred to 500 c.c. volumetric flask, and allowed to stand one week; 50 c.c. portions were used to determine sugar according to the Daufresne-O'Sullivan method. The weights of cupric oxid averaged 210 mg., or 72 per cent.

Ether Soluble Material.—1.6998 gm. of the powdered specimen was extracted with ether and the ether extract evaporated to dryness. The residue weighed 0.0600 gm., equivalent to 3.53 per cent.

SYPHILODAL AMPULES

Water.—The liquid from one ampule was distilled over very carefully. The freezing point of the liquid was +0.1° C., and it was neutral to methyl orange and phenolphthalein.

Arsenic.—The contents of one ampule was placed in a small florence flask, 20 c.c. of concentrated sulphuric acid added and heated to 70 C.; 0.5 gm. of potassium permanganate was added in small amounts. The procedure was then carried on as described by Engelhardt and Winters in *J. Am. Pharm. Assn.*, 1915, p. 1469. To the mixture from 5 to 10 c.c. of hydrogen peroxid solution were added drop by drop until the color had disappeared. The liquid was diluted with 20 c.c. of water, boiled fifteen minutes, diluted again and boiled fifteen minutes, then cooled and made up to exactly 100 c.c. A blank was also run alongside. Five c.c. of this solution was then tested quantitatively for arsenic according to the U. S. P. IX method, using all precautions. Comparisons of stains showed less than 0.00001 gm. of arsenic (As).

THE EXAMINATION OF CHLORIN-SODA AMPOULES

(Reprinted, with additions, from J. A. M. A., July 6, 1918, p. 39)

H. D. Dakin, in conjunction with A. Carrel and M. Daufresne, has introduced the so-called "Neutral Solution of Chlorinated Soda," or "Dakin's Solution," different standards and modes of preparation having been described. It is essentially a solution containing from 0.45 to 0.50 per cent. sodium hypochlorite, in a hypertonic solution of sodium chlorid and sodium carbonate and sodium bicarbonate. To prepare the solution, as they describe, requires that the available chlorin content of the chlorinated lime used be known, and that the available chlorin content of the finished solution be checked by titration. To obviate this, various preparations have been placed on the market, claiming to yield, when made according to direction, a solution having the correct strength of hypochlorite and to be "neutral" to phenolphthalein.

Johnson and Johnson offer "Chlorin-soda Ampoules" composed of (A), a sealed glass tube stated to contain 4.8 gm. liquid chlorin having a purity of "approximately over 99 per cent.," and (B), a sealed glass tube stated to contain 21.3 gm. monohydrated sodium carbonate U. S. P. The contents of "B" are placed in a 2.5 liter bottle, and dissolved in 1 liter of water. Tube "A," containing the liquid chlorin, is suspended from the inserted rubber stopper. The large bottle is then vigorously shaken, breaking the chlorin ampule.

Some of the claims made for the product are:

> "The Johnson and Johnson method in a few seconds gives the Carrel-Dakin antiseptic solution of standard strength of between 0.45 per cent. and 0.50 per cent. of sodium hypochlorite, free from caustic alkali.
>
> "All settling, decantation and filtering to eliminate lime sludge is avoided; the solution is exact and definite; all necessity for, and the trouble of an analytical test is obviated.
>
> "The Carrel-Dakin solution resulting from this method is perfectly clear and ready for immediate use.

"The method is thus at once adaptable to hospital and field use, as well as to ordinary office practice."

"It is not necessary to make analysis of the solution made up from liquid chlorin by the Johnson and Johnson method, but for those who wish to check up the strength we state that it must contain between 0.45 per cent. and 0.50 per cent. sodium hypochlorite and that this is determined by titrating 10 c.c., in the presence of an excess of potassium iodide and acetic acid, with tenth-normal sodium hyposulphite and that the amount of this hyposulphite solution necessary ranges between 12.0 c.c. and 13.4 c.c.

"The test for caustic alkalinity, as prescribed, consists in throwing some powdered phenolphthalein upon the surface of some of the solution in a beaker and twirling the beaker to mix it. No red color should be produced."

One original package containing three ampules each of chlorin and of "Soda Salts" was sent to the Council by Johnson and Johnson, and another original package was purchased on the open market.

The liquid chlorin was brown, and was contained in colorless hard glass ampules about 7 inches long and 3/8 inch in diameter. The following quantitative determinations were made:

Chlorin Ampule.—The chlorin was allowed to escape from one tube by opening the pointed end, with due precautions, by heating. The loss in weight of the ampule was 4.600 gm. chlorin. A very small yellow residue remained in the tube.

Sodium Carbonate Ampules.—The weight of the contents of four "soda" ampules was 21.7, 21.5, 21.6 and 21.5 gm., respectively; average, 21.5 gm.

By titration (*a*) 2.6336 gm. required 41.60 c.c. normal hydrochloric acid solution, equivalent to 97.98 per cent. monohydrated sodium carbonate; (*b*) 2.2295 gm. required 35.90 c.c. normal hydrochloric acid solution, equivalent to 99.70 per cent. monohydrated sodium carbonate; average, 98.9 per cent.

Sodium Hypochlorite Solution.—The directions given by Johnson and Johnson were followed in preparing the hypochlorite solutions. The titrations were also carried out according to the method described by Johnson and Johnson (essentially the U. S. P. assay method for Solution of Chlorinated Soda).

(A) The chlorin tube broke near the middle, developing pressure, and some chlorin escaped: (*a*) 10 c.c. of the solution required 9.88 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.37 per cent. sodium hypochlorite; (*b*) 10 c.c. of the solution required 9.88 c.c. tenth-normal sodium thiosulphate solution, equivalent to 0.37 per cent. sodium hypochlorite.

(B) In preparing this sample, the chlorin tube also broke above the level of the water. As the stopper of the bottle was wired down no chlorin could escape at once. Yet when the stopper was taken out, after the bottle had been shaken for about one minute, the strong smell denoted that some uncombined chlorin had escaped: (*a*) 10 c.c. required 10.35 c.c. tenth-normal sodium thiosulphate solution, equivalent to 0.38 per cent. sodium hypochlorite; (*b*) 10 c.c. required 10.16 c.c. tenth-normal sodium thiosulphate solution, equivalent to 0.38 per cent sodium hypochlorite.

(C) In preparing this sample, the chlorin tube broke near the lower end. After shaking the contents two minutes, no free chlorin escaped, when the stopper was released: (*a*) 10 c.c. of the solution required 13.3 c.c. tenth-normal sodium thiosulphate solution, equivalent to 0.49 per cent. sodium hypochlorite; (*b*) 10 c.c. required 13.3 c.c. tenth-normal sodium thiosulphate solution, equivalent to 0.49 per cent. sodium hypochlorite.

(D) The procedure was the same as C and no chlorin escaped: (*a*) 10 c.c. required 12.8 c.c. tenth-normal sodium thiosulphate solution, equivalent to 0.47 per cent. sodium hypochlorite; (*b*) 10 c.c. required 12.8 c.c. tenth-normal sodium thiosulphate solution, equivalent to 0.47 per cent. sodium hypochlorite.

(E) The solution was prepared as above, and after shaking from one and one half to two minutes, the stopper was released when chlorin escaped: (*a*) 10 c.c. required 12.8 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.47 per cent. sodium hypochlorite; (*b*) 10 c.c. required 12.8 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.47 per cent. sodium hypochlorite.

(F) This tube could not be broken when vigorously shaken inside of the large bottle. It was therefore removed, cleaned and dried, and the chlorin content determined as described above.

Stability of Solution after Forty-Eight Hours.—Solutions D and E were allowed to remain near a window on dark days for forty-eight hours. In solution D the strength of sodium hypochlorite was 0.46 per cent. In solution E there was no perceptible decrease.

Phenolphthalein Test.—All of the solutions gave no color with powdered phenolphthalein, as described by Dakin, although they did color an alcoholic phenolphthalein solution momentarily before it was destroyed.

DISCUSSION

If loss of chlorin is guarded against, Johnson and Johnson Chlorin-soda Ampoules will give a solution of the strength described by them. To insure this, the stopper should be wired down or otherwise secured firmly and the bottle shaken for at least two minutes after the chlorin ampule has been broken. As the chlorin is under considerable pressure, the ampules when broken, especially if the sealed end is short, are often greatly shattered so that due precaution should be taken to filter off the glass particles. The chlorin tubes would break easier, more surely and with less shattering of glass and less pressure, if the sealed end was either more uniformly drawn out to a longer and somewhat smaller point, or so modified that the breaking would occur at the narrow tip. (With regard to this, Johnson and Johnson write that precautions have been taken to draw out the point of the chlorin tube longer and finer, so that no trouble, on this account, will occur in the future.) As Johnson and Johnson state that the chlorin contained in the ampules has a purity of over 99 per cent., it would be a valuable contribution if they would publish purity tests for the chlorin.

As the result of the foregoing, the Council accepted "Chlorin-Soda Ampules J. and J.," describing them as follows:

CHLORIN-SODA AMPOULES.—Composed of a sealed glass tube stated to contain liquid chlorin (over 99 per cent. pure) 4.8 Gm. and a sealed glass tube stated to contain monohydrated sodium carbonate 21.3 Gm. and yielding, when the contents of the tubes are dissolved in 1,000 c.c. of water, a solution similar in composition to Neutral Solution of Chlorinated Soda.

To prepare the solution the contents of the tube of monohydrated sodium carbonate are placed in a bottle having a capacity of about 2,500 c.c. and dissolved in 1,000 c.c. water. The tube containing the liquid chlorin is suspended from a rubber stopper and is inserted into the bottle and the stopper firmly secured. The large bottle (after covering with a cloth) is shaken to break the chlorin tube. The contents of the bottle (without releasing the stopper) are then shaken for two minutes or longer. The solution, freed from particles of glass by decantation or filtration, is then ready for use, or its available chlorin may previously be checked by titration.

Actions, Uses and Dosage.—See Neutral Solution of Chlorinated Soda (New and Nonofficial Remedies, 1918, p. 154).

Manufactured by Johnson and Johnson, New Brunswick, N. J. U. S. Patent applied for. No U. S. trademark.

The finished solution contains from 0.45 to 0.50 per cent. sodium hypochlorite. The available chlorin content is determined by titrating 10 c.c. in the presence of an excess of potassium iodid and acetic acid, with tenth-normal sodium thiosulphate solution. For this titration 12.0 to 13.4 c.c. of tenth-normal sodium thiosulphate solution are required.

To determine if the solution contains an excess of alkali a small quantity of phenolphthalein is mixed by rotation with some of the solution contained in a beaker. No red color should be produced.

KATHARMON

(Abstracted, with additions, from the J. A. M. A., Aug. 10, 1918, p. 487)

In 1893 (when the publicatoin of "a formula" for proprietary medicines was thought to satisfy the requirements of scientific medicine) an advertisement in THE JOURNAL of the American Medical Association gave the following "formula" for Katharmon:

> "Hydrastis Canadensis, Phytolacca Decandra, Acid Salicylous C. P. (from Oil of Wintergreen), Acid Boric C. P., Mentha Arvensis, Thymus Vulgaris, Dist. Ext. Hamamelis Virg. Conc."

In 1907 an advertisement in the Kansas City *Medical Index-Lancet* declared that:

> "Katharmon represents in chemical combination the active principles of Hydrastis Canadensis, Gaultheria Procumbens, Hamamelis Virginica, Phytolacca Decandra, Mentha Arvensis, Thymus Vulgaris, with two grains C. P. Boric Acid to each fluid drachm."

Now the advertisements which appear in some medical journals state:

> "Katharmon represents in combination Hydrastis Canadensis, Thymus Vulgaris, Mentha Arvensis, Phytolacca Decandra, 10½ grains Acid Borosalicylic, 24 grains Sodium Pyroborate to each fluid ounce of Pure Distilled Extract of Witch Hazel."

A comparison of these so-called formulas shows that they have not only varied from time to time, but that in no instance was a quantitative statement with regard to all the asserted ingredients given.

The Council on Pharmacy and Chemistry having requested an examination of Katharmon, the Chemical Laboratory reported:

Katharmon has an alkaline reaction and therefore cannot contain boric acid, salicylic acid or "borosalicylic acid" (the latter is unknown to medical literature except as loosely applied to a simple mixture of boric and salicylic acids). The solution gives tests for sodium, borate, and salicylate and therefore probably contains sodium borate and sodium salicylate. Examined by the methods used for the determination of hydrastin in goldenseal preparations, a residue giving only a faint test for alkaloid was obtained; if present at all, hydrastis canadensis (goldenseal) is there only in very small amounts.

In publishing its report which discussed the composition of Katharmon and the claims made for it, the Council on Pharmacy and Chemistry noted that the Katharmon Chemical Company of St. Louis in advertising its Katharmon appeals especially to a profession whose members, should they live up to their ethical code, could not prescribe it, and called attention to the *Principles of Medical Ethics*, Sec. 6, Art. 1, Chapter II, ". . . It is equally unethical to prescribe or dispense secret medicines or other secret remedial agents. . . ."

Details of Analysis

Katharmon is a pale straw colored liquid with an aromatic odor.

Total Solids.—Twenty-five c.c. on evaporation and drying to constant weight on a water bath gave 1.2784 gm. residue, or approximately 5 gm. in 100 c.c.

Salicylic Acid.—Twenty-five c.c. were made acid and extracted with chloroform. The chloroform was allowed to evaporate spontaneously and the residue dried over sulphuric acid. The residue weighed 0.1967 gm. On titration with tenth-normal sodium hydroxid solution, 15.18 c.c. were used, indicating 0.2096 gm. salicylic acid.

Borate.—The usual ethyl borate test applied to some of the residue left on evaporation of Katharmon showed borate present.

Alkaloids.—Thorough extraction of 50 c.c. Kathamen with chloroform gave a residue weighing 0.0152 gm. The residue had a distinct odor of thymol or menthol. To the residue was added 7.68 c.c. fiftieth-normal acid; 7.3 c.c. fiftieth normal alkali were required to titrate back, leaving 0.38 c.c. fiftieth-normal acid neutralized by the residue. In another experiment 0.0049 gm. residue was obtained which did not neutralize any acid. In a third experiment 0.0055 gm. residue was obtained. In all cases, however, iodin, Mayer's, and picric acid solutions indicated traces of alkaloid.

BITRO-PHOSPHATE

Calcium Glycerophosphate at Sixteen Hundred Per Cent. Profit

(Reprinted, in part, with additions, from J. A. M. A., Sept. 14, 1918, p. 921)

Bitro-Phosphate is put on the market by the Arrow Chemical Co. of New York; it is recommended:

> **For neurasthenia, nervousness, irritability, depression, brain-fag, insomnia, debility, excessive thinness, general weakness, lack of physical energy and the usual ailments arising from nerve weakness and tissue wastage.**

With the trade-package comes a leaflet discussing, in language that may be counted on to duly impress the unscientific mind with its profundity, "The Relation of Organic Phosphorus to the Human Machine." Numerous quotations from medical literature follow, all of which, so far as they have been checked, relate, in the original, to calcium glycerophosphate. Not that there is any hint in the advertising that this well-known drug is the preparation to which the quotations refer; the reader is left to infer that they refer to "Bitro-Phosphate."

Because of the number of inquiries that have been received, and the extensive advertising of "Bitro-Phosphate," the preparation was taken up for examination in the Association's Chemical Laboratory. The chemist's report follows:

CHEMIST'S REPORT

Bitro-Phosphate comes in the form of uncoated tablets weighing 0.355 Gm. each (about $5\frac{1}{2}$ grains) and there are forty-two tablets in each package. The package sells for one dollar. The tablets, which had a somewhat bitterish saline taste and were odorless, slowly distintegrated in water but did not entirely dissolve. In dilute hydrochloric or dilute nitric acid the tablets dissolved readily with some effervescence. No chlorid, bromid, iodid, sulphate, phosphate, or hypophosphite could be detected by the ordinary tests. The solution in water or acid gave tests for calcium in abundance. The tablets on heating, gave off inflammable vapors and, when strongly heated, charred. The charred mass extracted with nitric acid gave the molybdate test for phosphate in abundance. This would indicate an organic phosphate. The U. S. P. tests for calcium glycerophosphate were applied to a solution of the tablet material in water and the tests were positive in every case. Six of these tablets when titrated by DuBois method are found to contain 1.9324 Gm. calcium glycerophosphate, or 0.322 Gm. (about 5 grains) per tablet.

The conclusion to be drawn from this examination is that Bitro-Phosphate is essentially a 5 grain tablet of calcium glycerophosphate.

Very simple! Calcium glycerophosphate can be purchased for $2.35 per pound. One pound of calcium glycerophosphate would make over thirty-three bottles of five-grain "Bitro-Phosphate" tablets, forty-two tablets to the bottle; thirty-three bottles of Bitro-Phosphate sell for $33.00! Does a profit of sixteen hundred per cent. come within the excess profit tax?

THE JOURNAL has discussed at different times the therapeutic value—or lack of value—of the glycerophosphates, and has shown the fallacy of the theory that organic phosphorus compounds are more readily assimilated than the inorganic phosphorus preparations. All that needs, further, to be said is that if the public wishes to take calcium glycerophosphate it may purchase it under its own name at a fraction of the price.

Details of Analysis

These tablets were white, odorless, with a rather saline, bitterish taste. They almost entirely dissolved in cold water, completely in dilute hydrochloric acid. The average weight of the tablets was 0.355 gm. or 5 ½ grains.

The tablets charred on application of heat, showing organic matter present.

Chlorid, Bromid, Iodin, Sulphate.—A solution of the tablets in dilute nitric acid did not precipitate with either silver nitrate or barium chlorid.

Phosphate.—A soluton of the tablets in dilute nitric acid did not precipitate with ammonium molybdate in the cold, but on boiling for a few minutes a yellow precipitate formed.

A solution in dilute nitric acid of the ash from one tablet gave with ammonium molybdate an abundant and characteristic precipitate for phosphate.

Metals.—By the usual methods calcium was the only metal found in appreciable quantities.

Calcium Glycerophosphate.—A solution of the tablets in water responded to all the tests of the U. S. P. given for calcium glycerophosphate. The quantity of calcium glycerophosphate was determined by the method of DuBois.[1] Six tablets when titrated by this method required 16.5 c.c. of half-normal hydrochloric acid, indicating 1.9325 gm. calcium glycerophosphate, or 0.322 gm. per tablet (5 grains is 0.324 gm.). In another trial 6 tablets required 16.2 c.c. half-normal hydrochloric acid.

Alkaloids.—Ten gm. of the powdered tablets examined by the method given under Sulpherb Tablets, p. 45, gave no reaction for alkaloids.

Bitro-Phosphate is then essentially 5-grain tablets of calcium glycerophosphate.

CAMPETRODIN AND CAMPETRODIN NO. 2

(Abstracted, with additions, from J. A. M. A., Sept. 21, 1918, p. 993)

"Campetrodin" and "Campetrodin No. 2, Double Strength," are two so-called "ethical medicinal specialties" of the A. H. Robins Company, Richmond, Va.

As regards the composition of these proprietaries, an advertisement in the *Maryland Medical Journal* (Dec., 1917) states:

> "CAMPETRODIN
> (Made in Two Strengths of Iodine)
> This preparation is an Oleaginous Solution of Iodine in Camphor."

A booklet describing the "ethical medicinal specialties" of the Robins Company contains the following in reference to Campetrodin:

> "Composition
> Camphor
> Iodine Element
> Oleaginous Solvent"

From these statements it appears that the preparations are claimed to contain elementary (free) iodin in an "oleaginous solvent." Since free iodin, as is well known, readily combines with fats, it was decided to determine the form in which the iodin was present in these preparations.

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[1] J. Indust. and Engin. Chem., 1914, p. 126.

The examination demonstrated that both preparations contained but a trace of free iodin. On steam distillation there was obtained from both preparations a distillate amounting to about 35 per cent. by volume which had an odor strongly suggestive of turpentine, while the residue contained the iodin and had the characteristics of an iodized fatty oil.

Quantitative determinations indicated that Campetrodin contained approximately 0.03 per cent. of free iodin and 1.3 per cent. of iodin in combination with the fatty oil. Campetrodin No. 2, Double Strength, contained approximately 0.03 per cent. free iodin and 2 per cent. of iodin in combination with the fatty oil.

This examination demonstrates that, contrary to the published statements, Campetrodin is not a preparation of free (elementary) iodin, and that Campetrodin No. 2, Double Strength, does not contain twice as much iodin as Campetrodin.

The report of the Laboratory's examination was submitted to the Council on Pharmacy and Chemistry by a referee who pointed out that the examination demonstrated that the statements made in regard to the composition of Campetrodin and Campetrodin No. 2 are incomplete in some respects and false in others. While in view of the Laboratory's findings an examination of the therapeutic claims of the preparation appeared superfluous to the referee, he noted that a solution containing practically no free iodin evidently is not, as claimed by the Robins Company, "adapted for use wherever . . . iodin is indicated externally . . ."

The Council declared Campetrodin and Campetrodin No. 2 inadmissible to New and Nonofficial Remedies because of false statements as to chemical composition and therapeutic action.

Details of Analysis

Both products were dark brown liquids having an odor strongly suggestive of turpentine. The specific gravity of Campetrodin at 15.6 degrees was found to be 0.9103 and of Campetrodin No. 2, 0.9394. The products were completely miscible with chloroform and ether, but only partially so with alcohol.

A. *Uncombined Iodin.*—Uncombined iodin was determined by shaking 10 c.c. of the products with potassium iodid solution, adding starch test solution and titrating the blue solution with tenth-normal sodium thiosulphate solution.

1. Ten c.c. (9.103 gm.) of Campetrodin required 2.0 c.c. one-hundredth normal sodium thiosulphate solution (0.9505) equivalent to 0.0024 gm. of iodin or 0.026 per cent.

2. Ten c.c. (9.394) of Campetrodin No. 2 required 2.5 c.c. one-hundredth normal sodium thiosulphate solution (0.9505) equivalent to 0.0029 gm. iodin or 0.03 per cent.

B. *Total Iodin.*—Total iodin was determined by Kendall's Method (*J. Am. Chem. Soc.*, 1912, p. 894) which consists in fusing with sodium hydroxid, destruction of organic matter by the addition of potassium nitrate, oxidation to iodate by the addition of sodium hypochlorite, liberation of iodin by potassium iodid titration of the liberated iodin with sodium thiosulphate solution. The number of cubic centimeters consumed divided by 6 gives the equivalent amount of sodium thiosulphate.

Campetrodin

1. 4.5515 gm. (5 c.c.) of Campetrodin required 4.9 c.c. tenth-normal sodium thiosulphate solution (0.9505) equivalent to 0.0589 gm. iodin or 1.29 per cent.

2. 4.5515 gm. (5 c.c.) of Campetrodin required 4.8 c.c. tenth-normal sodium thiosulphate solution (factor 0.9505) equivalent to 0.0577 gm. iodin, or 1.28 per cent.

Average: 1.285 per cent. total iodin.

Campetrodin No. 2

1. 4.697 gm. (5 c.c.) of Campetrodin No. 2 required 7.45 c.c. of tenth-normal sodium thiosulphate solution (factor 0.9505) equivalent to 0.0905 gm. iodin or 1.92 per cent.

2. 4.697 gm. (5 c.c.) of Campetrodin No. 2 required 8.4 c.c. tenth-normal sodium thiosulphate solution (factor 0.9505) equivalent to 0.1000 gm. iodin or 2.13 per cent.

Average: 2.025 per cent. total iodin.

Steam Distillation.—The products were steam distilled in the usual manner, collecting the distillate in a graduated receiver so that the volume of volatile oil could be read off directly. Thus 20 c.c. of Campetrodin and Campetrodin No. 2 each yielded 7 c.c. of "volatile oil," or 35 per cent. by volume. The "volatile oil" was light yellow in color and had an odor strongly suggestive of turpentine.

The residue remaining in the distillation flask was a dark-brown viscous oil, containing the iodin. It was almost completely saponifiable with alcoholic potash.

EATONIC

(Abstracted, with additions, from The Journal, A. M. A., Sept. 21, 1918, p. 993)

Eatonic is distributed by Eatonic Remedy Company, 1018 S. Wabash Ave., Chicago, Ill. It is in the form of tablets. These are black, uncoated, having a mint like odor, and a sweet and mint like taste. Each tablet is stamped with the monogram EATONIC and each weighs about 27.4 grains.

The package is a card board box with tin top and bottom, containing forty-four tablets. On this box it is stated that

> "Eatonic, for your stomach's sake" is "A modern medicine for daily use"; "Dyspepsia, Nausea, Sour Stomach, Fermentation, Heartburn, and Mal-assimilation of food, all forms of Stomach and Digestive Disturbances caused by Acidity." "To help the appetite and digestion, eat them. . . Eat one or two Eatonics before each meal."

The package contains a circular, a sample of pills called OMI a "new treatment for liver and bowels," and three envelopes for carrying Eatonic on the person all the time.

The circular in the package mentions about all the ills the stomach is heir to as being "relieved," "removed," or "prevented" by Eatonic. Also the morning sickness or vomiting in pregnancy is "relieved" by it. If the good results from Eatonic are retarded it is due to "liver or bowel trouble." So take OMI, the circular suggests.

A qualitative examination showed Eatonic to contain calcium, magnesium, carbonate, sugar, charcoal, and silica or a silicate. The odor and taste suggested peppermint. No soluble carbonate could be detected, therefore the calcium and carbonate are probably present as calcium carbonate.

The qualitative examination, then, indicates that Eatonic is essentially calcium carbonate, charcoal, sugar, and oil of peppermint as flavoring. The quantitative examination which follows bears out this conclusion.

Chemical Examination of Eatonic

QUALITATIVE

Metals.—Upon incinerating Eatonic an ash is obtained which when examined by the usual method was found to contain traces of iron, aluminum, abundance of calcium, appreciable quantities of magnesium, and large quantities of silica (matter insoluble in hydrochloric acid).

Heavy Metals.—These were not found. The acid solution of the residue after ignition does not precipitate with hydrogen sulphid and also the solution after making alkaline with ammonia showed no coloration with hydrogen sulphid.

Acids.—No acid radicals except traces of chlorid could be detected in the above described residue.

Sugar.—A quantity of Eatonic triturated with water and filtered gave a neutral solution which did not reduce Fehling's solution. On warming this solution with a drop or two of hydrochloric acid it promptly reduced Fehling's solution.

Charcoal.—The black material present in Eatonic is not decomposed by acids, or alkalies, or by any other reagents used at any time in the analysis. It is readily burned away by strong heat, however.

Carbonate.—When acids are added to Eatonic affervescence takes place. The gas was identified as carbon dioxid by the usual tests.

Alkaloids, Synthetic Drugs, Etc.—Eatonic was extracted with chloroform and the chloroform allowed to evaporate spontaneously. A slight oily residue was obtained which had the odor of mint. No crystalline substances were present.

On further extracting the Eatonic with alcohol and evaporating the alcohol on a waterbath, a slight residue was obtained which was sweet, soluble in water, and on warming with acids reduced Fehling's solution. Sugar is slightly soluble in alcohol, therefore this seemed to be sugar.

Neither residue gave reactions for alkaloids.

QUANTITATIVE

Ash.—Two gm. Eatonic were heated to constant weight in the flame of a Meeker burner; 0.3950 gm., or 19.75 per cent. of residue was obtained.

Silica.—The residue was heated with hydrochloric acid and the insoluble portion collected on an ashless filter and well washed. After drying it was ignited. The residue weighed 0.1145 gm., indicating 5.73 per cent. silica.

Iron and Aluminum.—The combined filtrate and washings from the silica was made alkaline with ammonia water and boiled a few minutes. The precipitated aluminum and iron was collected and ignited in the usual way, and the residue weighed 0.0225 gm., indicating 1.13 per cent. iron and aluminum oxid.

Calcium.—In the filtrate and washings from the iron and aluminum the calcium was determined by precipitation with oxalate in the usual manner. The calcium oxid obtained weighed 0.2180 gm., indicating 10.90 per cent. calcium oxid.

Magnesium.—In the filtrate from the calcium oxalate precipitate magnesium was determined as magnesium hypophosphate in the usual manner. The $Mg_2P_2O_7$ obtained weighed 0.1110 gm., indicating 2.01 per cent. magnesium oxid.

Summary of foregoing:

	Per Cent.
Total ash ....19.75 per cent.	
Silica	5.73
Iron and aluminum oxid.............	1.13
Calcium oxid	10.90
Magnesium oxid	2.01
	19.77

Carbon Dioxid.—Carbon dioxid was determined by aid of the usual Knorr apparatus: 5.0191 gm. Eatonic gave 0.4353 gm. CO_2, or 8.67 per cent. In a duplicate, 5.0885 gm. Eatonic gave 0.4245 gm. CO_2, or 8.34 per cent.; average 8.51 per cent. CO_2.

Calcium Carbonate.—Since calcium carbonate is 56 parts CaO and 44 parts CO_2 this relationship should exist between the calcium oxid and carbon dioxid found, if all the calcium in Eatonic is present as carbonate. Since the per cent. CaO was 10.90 and the per cent. CO_2, 8.51, which is in the proportion of 56.07 to 43.74, the calcium and the carbonate must be present as calcium carbonate.

Sugar.—2.3002 gm. Eatonic were added to about 50 c.c. 10 per cent. hydrochloric acid and the mixture heated to about 70 C. for a short time. The insoluble matter was collected in a tared Gooch crucible and the filtrate made alkaline with sodium carbonate. The precipitate calcium carbonate was filtered off and the filtrate made up to 500 c.c. with distilled water. In this solution sugar was determined by the method given in Leach, Food Inspection and Analysis, Ed. 3, 1913, p. 591. Ten c.c. Fehling's solution required for complete reduction 18.5 c.c. of this sugar solution, indicating 55.81 per cent. sugar.

Charcoal.—The insoluble portion obtained in the determination of sugar was dried at 100 C., weighed, and ignited. The loss was 0.2635 gm., indicating 11.46 per cent. carbon.

Moisture.—1.0286 gm. dried to constant weight at from 98 to 100 C. lost 0.0210 gm., indicating 2.04 per cent. matter volatile at 100 C.

Oil.—On extracting 4.5745 gm. Eatonic with chloroform and allowing the chloroform to evaporate spontaneously, an oily residue weighing 0.0469 gm., or 1.03 per cent., was obtained.

SUMMARY OF THE ANALYSIS

	Per cent.
Silica	5.73
Iron and Aluminum oxid	1.13
Calcium oxid	10.90
Magnesium oxid	2.01
Carbon dioxid	8.51
Sugar	55.81
Charcoal	11.46
Volatile at 100 C.	2.04
Undertermined	2.41
	100.00

From this analysis we conclude that Eatonic is essentially calcium carbonate, 20 per cent., sugar 55 per cent., charcoal 12 per cent. Each tablet contains approximately 5.5 grains calcium carbonate, 15 grains sugar, 3.25 grains charcoal.

SULPHERB

(Reprinted, with additions, from J. A. M. A., Oct. 26, 1918, p. 1431)

"Sulpherb" or "Sulpherb Tablets" is another of the multifarious nostrums sold by the Blackburn Products Company of Dayton, Ohio. In common with their class, they are advertised by the "fake prescription" method, a scheme which gives the reader the impression that the advertisement is really a newspaper "health department." The individual used by the Blackburn concern to carry out this deceit is Lewis Baker, whose activities in this connection we have previously noted. The advertisements appear under the general title, "The Doctor's Advice, by Dr. Lewis Baker." Here are samples of the method by which the public is deceived:

> "*L. W. writes:* 'My blood is in bad condition. I suffer with constipation and my tongue is always coated. My skin is dark and I have pimples. I feel tired all the time, but I am too nervous to sleep. Please prescribe.'
>
> "ANSWER: Get a tube of three-grain sulpherb tablets (not sulphur) and take according to directions. They will clean your blood, aid digestion, and relieve constipation. When you get your blood pure, the other symptoms disappear."
>
> "*George asks:* 'For several months I have not been feeling well. My skin is sallow, my tongue coated, have headache, am sleepless, nervous and bothered with chronic constipation. Please help me.'

"ANSWER: You need a laxative blood cleansing treatment in the form of three-grain sulpherb tablets (not sulphur). Overcome the tendency to constipation and gradually your good health and pure blood will return."

"*Orrie writes:* 'I have been taking salts to purify my blood and cure my skin of itching and pimples, but don't get much benefit. Please prescribe for this.'

"ANSWER: I advise three grain sulpherb tablets (not sulphur tablets), composed of sulphur, cream of tartar and vegetable extracts that remove constipation and purify the system. Take this treatment for several months for best results."

The package in which "Sulpherb Tablets" comes bears on the label one of those noninformative, alleged formulas that the shrewd "patent medicine" faker so delights in. No quantities are given, but the public is told that the tablets "contain the extracts or concentrations of Cascara, Aloes, May Apple, Nux-Vomica, Black Cherry, Capsicum, Ginger, Sarsaparilla. Also Calcium Sulphide, Sulphur and Cream of Tartar."

"Sulpherb Tablets" were examined in the A. M. A. Chemical Laboratory, and the chemists report as follows:

"Sulpherb Tablets" are sugar coated, yellow, and weigh about 7.3 grains each, coating and all. The package states that they are three grain tablets; this probably refers to the medicament only. A qualitative examination shows the presence of emodin-bearing drugs, the taste suggesting aloes. Sulphur, calcium, sulphid, traces of alkaloid, potassium, and tartrate are present. The chemical examination shows that "Sulpherb Tablets" are probably compounded from calcium sulphid, sulphur, cream of tartar, and vegetable extractives. Of the vegetable extractives claimed to be present, aloes was indicated and a trace of some alkaloid, the amount of which was too small to permit its identification. If this alkaloid is strychnin, the quantity is insignificant, certainly not more than 1/1000 of a grain to each tablet.

Here we have, then, a simple laxative tablet, consisting essentially of drugs that have been known and used for generations, both by the medical profession and by the public. It is advertised in a way that is doubly deceitful. First the public is deceived by being led to infer that "Sulpherb Tablets" are extraordinarily efficacious; then it is further deceived by the fakish "health column" and the concealment of the "patent medicine" character of the nostrums that are recommended. Newspapers that accept such advertisements commit more than an offense against the public health; they are, for a consideration, guilty of imposing on the public's confidence by leading their readers to suppose that the "Health

Talk" or "Doctor's Advice" is a department of the paper, presenting unbiased information on health subjects. The whole "prescription fake" scheme is a disgraceful combination of nostrum exploitation, quackery and low-grade advertising.

Details of Analysis

Twenty-five tablets weighed 11.8825 gm., or 0.475 gm. per tablet or about 7.3 grains.

Sulphid.—A small quantity of the crushed tablets was placed in a small flask and diluted hydrochloric acid added. Effervescence was noted. The gas given off had the odor of hydrogen sulphid and blackened paper moistened with lead acetate solution.

Sulphur.—A quantity of the crushed tablets was triturated with chloroform. The chloroform poured off and allowed to evaporate. Characteristic crystals of sulphur were obtained. These crystals also burned with the odor of sulphur dioxid.

Heavy Metals.—A quantity of the crushed tablets was heated for some time with hydrochloric acid. The acid solution gave no precipitate with hydrogen sulphid. After making alkaline with ammonia and filtering out the slight precipitate formed, the alkaline filtrate gave no precipitate with hydrogen sulphid.

Calcium.—The alkaline solution from the heavy metal test gave an abundant precipitate with ammonium carbonate. This precipitate dissolved in hydrochloric acid and made alkaline with ammonia gave an abundant precipitate with ammonium oxalate.

Magnesium.—A small portion of the filtrate from the precipitate calcium carbonate gave a slight precipitate with sodium phosphate.

Potassium.—The filtrate from the precipitated calcium carbonate was evaporated to dryness and the ammonium salts expelled. The residue was heated with water and the solution filtered off. This solution gave a yellow precipitate with sodium cobaltic nitrite and a white crystalline precipitate with tartaric acid solution and a little alcohol.

Tartaric Acid.—Ten tablets were ground and triturated with water. To this mixture sulphuric acid was added until in excess. The hydrogen sulphid was expelled by heat and the calcium sulphate filtered out and washed with hot water. To the filtrate was added potassium chlorid and about one sixth its volume of alcohol. Considerable white crystalline precipitate settled out. This precipitate gave a solution in water that was acid and the solution when neutralized with ammonia gave a precipitate with silver nitrate. This mixture with a drop or two of ammonia gave a fine silver mirror on application of heat.

Alkaloids.—Ten tablets were finely powdered and mixed with about 10 gm. fine sand. Twenty c.c. chloroform were then added and the mixture shaken frequently during ten minutes. Ammonia water in distinct excess was then added and the mixture shaken frequently during six hours. The chloroform was then decanted and the residue washed with four portions, 10 c.c. each, of chloroform. The chloroform was allowed to evaporate. The residue was then washed with tenth-normal acid and the acid solution filtered into a separator. This solution was made alkaline and extracted with chloroform. The chloroform was allowed to evaporate and the residue dissolved in fiftieth-normal acid and the excess acid titrated back with fiftieth-normal alkali. No acid was consumed by the residue, therefore no appreciable quantity af alkaloid could be present. The solution obtained here gave a slight cloudiness with Dragendorff's bismuth iodid reagent, indicating the possible presence of traces of alkaloid.

Emodin.—Five tablets were crushed and extracted with repeated small quantities of water. The aqueous solution was acidulated and shaken with benzol. The benzol solution was then shaken with dilute ammonia. The ammonia was distinctly colored, brownish-pink.

THE STANDARDIZATION OF PROCAIN AND EXAMINATION OF THE MARKET SUPPLY

(Reprinted, in part, with additions, from J. A. M. A., Jan. 11, 1919, p. 136)

Procain, which chemically is the mono-hydrochlorid of Para-amino-benzoyldiethyl-amino-ethanol, is the nonproprietary name selected by the Federal Trade Commission as the official designation for the drug previously known under the proprietary name "novocaine." Before the war procain was obtainable in this country only through the

Farbwerke Hoechst Co., the American representative of the German establishment, Farbwerke, vorm. Meister, Lucius and Bruening, under the name "novocaine." This monopoly on "novocaine" was exercised by virtue of United States patent No. 812,554, which was issued to Alfred Einhorn, Munich, Germany, assignor to Farbwerke, vorm. Meister, Lucius and Bruening, Hoechst a. M., in 1906. With the outbreak of hostilities, Congress passed the Trading with the Enemy Act, and under this, the Federal Trade Commission took charge of the novocain patent with a view of securing the production of this product in the United States. To ensure an adequate supply of the drug, the Federal Trade Commission on recommendation of the Committee on Synthetic Drugs of the National Research Council, in addition to issuing a license to the Farbwerke Hoechst Company (which license was later transferred to the H. A. Metz Laboratories) granted authority to the Abbott Laboratories and the Rector Chemical Company to manufacture it under the U. S. patent after specimens submitted by these firms had been found satisfactory in the Association's Laboratory and at the Cornell Pharmacologic Laboratory.

When the first specimen of American made procain was sent to the American Medical Association Chemical Laboratory it was necessary to work out adequate standards. The standards were formulated on the basis of the novocain monograph in the German Pharmacopoeia, 1910, Ed. 5, p. 363, Remedia "Hoechst," p. 242, and New and Nonofficial Remedies, 1918, p. 32, and the work carried out in this Laboratory.

The following description has been adopted for New and Nonofficial Remedies, 1919, and all specimens of procain were subjected to these tests:

Procain occurs in small colorless and odorless crystals, or a crystalline powder which if placed on the tongue produces a transient sense of numbness.

It melts at 153-155 C.[1]

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[1] U. S. patent number 812,554—the novocain patent—declares that the salt melts at 156 C. Evidently based on this, the German Pharmacopoeia Remedia "Hoechst" and past editions of New and Nonofficial Remedies give this melting point. Two specimens of German made novocain obtained from our files, stated to be manufactured by Farbwerke-Hoechst vorm. Meister, Lucius and Bruening, Hoechst a.M. were found to melt respectively between 154 and 155 C. and between 153.5 and 154.5 C. when the melting point was determined according to the directions of the U. S. Pharmacopoeia, 9th revision. The various specimens examined at that time melted between 153 and 155 C. and it was decided to permit this range.

One gm. of procain is soluble in 0.7 c.c. of water and in 20 c.c. of alcohol U. S. P. (95 per cent.) at 20 C. From the aqueous solution, which is neutral, alkali hydroxids and carbonates precipitate the free base in the form of a colorless oil, which soon congeals to a crystalline mass, but solutions of sodium bicarbonate are miscible with solutions of procain without producing precipitations or turbidity.

Dissolve 1 gm. of procain in water. Separate portions of the solution yield a white precipitate with potassium mercuric iodid solution, a white precipitate with murcuric chlorid test solution, a brown precipitate with iodin test solution and a yellow precipitate with picric acid test solution. Acidify a portion with dilute nitric acid. A white curdy precipitate is thrown down on the addition of silver nitrate test solution.

Dissolve about 0.1 gm. of procain in 5 c.c. of water, add 2 drops of dilute hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent.) and mix with a solution of 0.2 gm. of betanaphthol in 10 c.c. of sodium hydroxid solution (10 per cent.). A scarlet red precipitate is thrown down.

To a solution of about 0.1 gm. of procain in 5 c.c. of water add 3 drops of dilute sulphuric acid and mix with 5 drops of potassium permanganate test solution. The violet color of the latter disappears immediately (distinction from cocain).

Dissolve about 0.1 gm. procain in 1 c.c. sulphuric acid U. S. P. The solution is colorless (organic impurities).

Dissolve 0.1 gm. of the salt in 10 c.c. of water and saturate with hydrogen sulphid. No coloration or precipitation occurs (salts of the heavy metals).

Incinerate about 0.5 gm. of procain accurately weighed. Not more than 0.1 per cent. of residue remains.

To obtain specimens representing the market supply, orders for the three brands of procain were placed with pharmaceutical firms in New York, Baltimore and San Francisco. The Baltimore and San Francisco firms supplied specimens of procain-novocain brand and procain-Rector brand but reported that the Abbott brand was not procurable. The New York correspondent was able to supply procain-Rector only. As the entire output of the Abbott Laboratories was stated to go to the Government, specimens of this product were obtained through the Surgeon-General of the Army from the General Purchasing Office, Medical Dept., U. S. Army. The following specimens were obtained and examined:

1. Procain-Abbott, 6 specimens: The first specimen bore no serial number but the five later specimens were designated respectively, No. 89999, No. 89998, No. 89997, No. 89996, and No. 810995 representing batches from which shipments are to be made on contracts placed by the General Purchasing Office, Medical Department, U. S. Army, with the Abbott Laboratories of Chicago.

2. Procain-novocain brand, 4 specimens: These were designated respectively, A56, A57, A63, and A67. The first two specimens were labeled "Manufactured by the Farbwerke-Hoechst Co. at the H. A. Metz Laboratories." The third specimen (not in original container) was labeled "H. A. Metz Laboratories" and the fourth was marked "Manufactured by the H. A. Metz Laboratories."

3. Procain-Rector, 3 specimens: Each bore the statement "Manufactured by the Rector Chemical Company" but had no "lot number."

From this examination it appears that all the specimens of procain received complied satisfactorily with all tests of identity and purity with the following exceptions: (1) One specimen of procain-Abbott had a melting point slightly below the permitted range; however, the last five specimens had the required melting point. (2) Five specimens of procain-Abbott and the last three specimens of procain-Rector were not entirely colorless, but had a yellow or light brown tinge.

The toxicity experiments which were carried out by Dr. R. A. Hatcher of the Cornell Pharmacologic Laboratory, were reported as being satisfactory.

When the Council on Pharmacy and Chemistry referred the matter of the discolored specimens of procaine to the Rector Chemical Company for explanation, the firm wrote that for a short time for some unexplainable reason its procain had been slightly yellowish in color, but that every batch had been carefully tested and found to answer all chemical requirements. The firm stated that the product which it had sent out for some time past had been white and yielded a colorless solution.

To a like inquiry from the Council the Abbott Laboratories replied that the five samples which were found discolored were products manufactured by the Rector Chemical Company and represented goods which it had purchased to assist in filling delayed orders, because the firm had found itself unable to keep pace with the demand on account of delay in

In the accompanying table the results of the examination are given. For comparison the findings for the specimens examined previously are included.

Brand	Date Received	Color	Melting Point	Ash
Procain (Abbott), from Committee on Synthetic Drugs....	12/21/17	White	154-155 C.	None
Procain (Abbott), submitted to Council P. and C.	1/29/18	White	153.5-154.5 C.	None
Procain (Abbott), Gen. Pur. Off. U. S. Army................	8/31/18	White	152.5-153.5 C.	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89999.....	9/30/18	Slight brownish tint	153-154.5 C.	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89998.....	9/30/18	Slight brownish tint	153-154.5 C.	0.005%
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89997.....	10/ 8/18	Slight brownish tint	153-154 C.	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 89996.....	11/ 4/18	Slight brownish tint	153.5-154.5 C.	None
Procain (Abbott), Gen. Pur. Off. U. S. Army, No. 810995....	11/ 4/18	Slight brownish tint	153.5-154.5 C.	None
Procain (Farbwerke Hoechst Co.), submitted to Council....	10/24/17	White	153-154 C.	None
Procain (Farbwerke Hoechst Co.), submitted to Council....	12/10/17	White	153-154.5 C.	None
Procain (Farbwerke Hoechst Co.), submitted to Council, market spec. "A56"...........	8/ 9/18	White	153.5-154.5 C.	None
Procain (Farbwerke Hoechst Co.), submitted to Council, market spec. "A57"...........	9/ 9/18	White	153.5-154.5 C.	None
Procain (H. A. Metz Lab.), market spec. "A63"...........	8/23/18	White	153-154 C.	None
Procain (H. A. Metz Lab.), market spec. "A67"...........	9/23/18	White	153-154 C.	0.018%
Procain (Rector), from Com. on Synthetic Drugs...........	12/18/17	White	153-154.5 C.	None
Procain (Rector), market spec.	8/20/18	Slight brownish tint	153-155 C.	None
Procain (Rector), market spec.	8/23/18	Slight brownish tint	153-155 C.	None
Procain (Rector), market spec.	8/23/18	Slight brownish tint	153-154.5 C.	None

securing needed apparatus. The firm submitted protocols to show that the procain made by it, by Rector and by Metz were of equal toxicity.

So far as the evidence goes, there was nothing to indicate that the yellowish or brownish colored specimens of procain were seriously impure. On the contrary, the compliance with the chemical and toxicologic tests indicated that the color was due to an insignificant trace of some colored substance produced in the manufacturing process. In view of this, the Council considered the use of the discolored product to be justified in the present emergency, although it urged that the future supply of procain should be free from color and also comply to the the tests of purity. It made this request in the interest of the medical and dental professions, which use the drug, and also in a desire that in the manufacture of synthetic drugs, the United States should occupy a high place.

of
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PART III

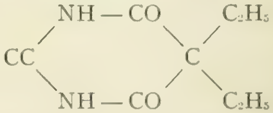
REPORTS NOT PREVIOUSLY PUBLISHED

BARBITAL

During the year 1918, the laboratory examined several specimens of barbital, some of which were sent through the agency of the Federal Trade Commission and the Committee on Synthetic Drugs of the National Research Council; others were submitted to the Council on Pharmacy and Chemistry, which in turn asked the laboratory to examine the products.

Barbital was introduced into medicine under the proprietary name "Veronal" and as such was manufactured in Germany by Friedr. Bayer and Co., Leverkusen, and E. Merck and Co., Darmstadt, Germany. Barbital is described in New and Nonofficial Remedies, 1918, as diethylbarbituric acid.

(Diethylmalonyl urea)



It is official in the British Pharmacopoeia under the name "Bartitonum" and in the German Pharmacopoeia as "Acidum Diethylbarbituricum." Barbital "may be prepared by the interaction of esters of diethylmalonic acid with urea in the presence of metallic alcoholates; it is also obtained by condensation of diethyl-cyanacetic ester with urea by means of sodium alcoholate."[1] It is used in medicine chiefly as a hypnotic.

The tests given for diethylbarbituric acid may be condensed as follows:

> It is a white crystalline powder melting at "about 188 C." (N. N. R., 1918), "190 and 191 C." (German Pharm.), 191 C. (Brit. Pharm.). It is inodorous, has a faintly bitter taste and an aqueous solution is neutral or very slightly acid to litmus paper.

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[1] New and Nonofficial Remedies, 1918, page 95.

It is soluble in about 150 parts of cold water and in about 12 parts of boiling water. It is quite soluble in ether, acetone, alcohol and ethyl acetate; also somewhat soluble in chloroform, petroleum benzin, acetic acid and amyl alcohol. It is soluble in an aqueous sodium or potassium hydroxid solution, forming salts.

Prolonged heating with sodium carbonate solution liberates ammonia. When fused with caustic alkali ammonia is evolved,[2] and when the cooled residue is dissolved in water and the solution acidified with diluted sulphuric acid, carbon dioxid is liberated and a characteristic odor resembling that of fatty acids is developed.

Denige's reagent produces a white precipitate; in solutions acidified with dilute nitric acid, Millon's reagent produces a precipitate soluble in an excess of the reagent.

Diethylbarbituric acid, when heated carefully in a platinum dish, should be reduced to an ash without carbonizing. The ash should not be more than 0.1 per cent.

The different brands of Barbital which were submitted to the A. M. A. Chemical Laboratory were subjected to the foregoing tests. The products were:

1. Barbital (Abbott)—Sample A to Fed. Trade Com.
2. Barbital (Abbott)—Sample B to Fed. Trade Com.
3. Barbital (Abbott)—Sample C to Red Cross.
4. Barbital (Antoine Chiris) to Fed. Trade Com.
5. Barbital (V. Halter) to Fed. Trade Com.
6. Barbital (Rector Chem. Co.) to Fed. Trade Com.
7. Diethylbarbituric Acid (Merck) to Council.
8. "Veronal" manufactured by Farb. vorm. Fried. Bayer & Co., Germany.

All of these products responded satisfactorily; below are given the respective melting points and percentage of ash found. (The melting point of a mixture of the sample with the original "Veronal" was also always taken.)

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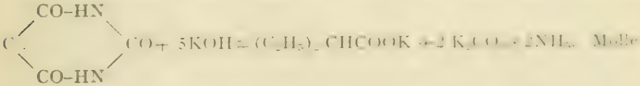
[2] According to B. Molle (Arbeiten aus dem Pharmaceutischen Institute, Universitat Berlin **2**: 160, 1904), the reaction is $(C_2H_5)_2$



$(C_2H_5)_2C\begin{array}{c}CO-HN\\ \\ CO-HN\end{array}CO + 5KOH = (C_2H_5)_2CHCOOK + 2K_2CO_3 + 2NH_3$. Molle converted some of the potassium diethylacetic acid to a silver salt, then determined the amount of silver in this sjlver salt. The theoretical percentages agreed with that found, which was confirmatory evidence of the general structure of "Veronal." Molle also describes the chemical data in connection with the physiologic work of H. Kleitt (ibid, p. 162). H. Lucas gives a few tests for diethylbarbituric acid (Pharm Jour. **93**: 424).

	MELTING POINT	Ash
1.	188.5-189.0	0.01
2.	188.5-189.0	0.01
3.	188.0-189.5	0.01
4.	188.0-188.5	0.04
5.	188.0-188.5	0.01
6.	188.0-188.5	0.01
7.	188.0-188.5	0.01
8.	188.0-188.5	0.02

Diethylbarbituric acid does not seem to form an insoluble salt with chlorplatinic acid; or an ether insoluble hydrochlorid or oxalate; nor an insoluble barium salt. It does not respond to many urea tests and is not affected by urease as would be expected in the light of the extensive investigations made by Van Slyke and Cullen on this enzyme.

As Barbital is also sold in the form of tablets or mixtures, a reliable method for its quantitative determination in presence of other substances is needed. Some experiments in this direction were made, but the press of other work did not permit their continuation. When time permits this work will be resumed.

At the time of writing this article, licenses for manufacture had been granted by the Federal Trade Commission to the Abbott Laboratories, Antoine Chiris and Rector Chemical Co.

Barbital-Sodium

Barbital-Sodium, formerly sold under the proprietary names "Veronal-Sodium" and "Medinal," is, as the first name suggests, the sodium salt of diethylbarbituric acid. Its advantages are stated to be that more rapid results are obtained because of its increased solubility over Barbital alone.[3] Barbital-Sodium should yield, according to theory, 11.17 per cent. sodium and 89.33 per cent. diethylbarbituric acid. A number of years ago when "Veronal-Sodium" and "Medinal" were being introduced, Puckner and Hilpert[4] found that these products corresponded closely to the theoretical amounts of sodium and diethylbarbituric acid. A recent examination of Veronal-Sodium, Merck, which had been submitted to the Council on Pharmacy and Chemistry, showed it to be the same composition previously reported.

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[3] See New and Nonofficial Remedies, 1918, p. 96.

[4] Puckner, W. A., and Hilpert, W. S.: Veronal-Sodium and Medinal. J. A. M. A., Jan. 23, 1909, p. 311; Reports A. M. A. Chemical Lab. **2**: 13, 1909.

So far, only one firm has endeavored to procure a license for the manufacture of the sodium salt. The product was submitted to the Laboratory, but because of the unsatisfactory results, it was not recommended for license, nor, as far as we are aware, has the firm investigated its anomalies.[5]

EXAMINATION OF BARBITAL-SODIUM

Moisture.—*Barbital-Sodium* was dried at 120 C. for three hours. The loss in weight was 0.04 per cent.

Sodium.—Barbital-Sodium (1 gm. sample) yielded sodium sulphate, equivalent to (*a*) 10.94 per cent. sodium and (*b*) 10.97 per cent. sodium. Puckner and Hilpert (Lab. Rep., 1909, p. 14) found 11.02 per cent. sodium in Medinal and 11.01 per cent. sodium in Veronal-Sodium. The theoretical amount according to formula given for Medinal by the proprietors, $(C_2H_5)_2CCONNaCONHCO$, is 11.17 per cent. The sodium in Barbital-Sodium is about 98 per cent. of the theoretical amount.

Diethylbarbituric Acid.—The method of obtaining the diethylbarbituric acid was by acidifying an aqueous solution containing a weighed quantity of Barbital-Sodium with hydrochloric acid. The freed acid was extracted in a separatory funnel with three different portions of ether, and the ether extract evaporated. The residue was dried at from 90 to 100 C. and weighed.

In case of Barbital-Sodium it was found that the amount of diethylbarbituric acid extracted varied, depending directly on the length of time between acidification and extraction.

(*a*) When shaken immediately with about 25 c.c., 15 c.c., and 15 c.c. portions of redistilled ether, 1.8966 gm. yielded 1.4316 gm., or 75.5 per cent. When the acidified solution was further extracted with ether, about three-quarters of an hour later, an additional amount, 0.1293 gm. diethylbarbituric acid was obtained, bringing the total to 82 per cent. Both fractions melted at from 188 to 189 C.

(*b*) When extracted immediately with ether 1.0488 gm. yielded 0.7208 gm. diethylbarbituric acid, or 68.7 per cent.

(*c*) When the ether layer was removed about one and one-half hours after acidification, 0.5924 gm. yielded 80.5 per cent. diethylbarbituric acid.

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[5] In testing the "Barbital-Sodium" it was considered that the quantitative separation into sodium sulphate and diethylbarbituric acid, the latter conforming to the test for Barbital, and the estimation of the moisture would be sufficient.

(*d*) When the ether layer was removed about four hours after acidification, 1.0000 gm. yielded 82.82 per cent. diethylbarbituric acid.

(*e*) When the ether layer was removed about four hours after acidification, 1.0000 gm. yielded 83.56 per cent. diethylbarbituric acid.

(*f*) When the ether layer was removed about four hours after acidification, 1.0000 gm yielded 83.41 per cent. diethylbarbituric acid.

Puckner and Hilpert found 88.77 and 89.18 per cent. diethylbarbituric acid in Veronal-Sodium, shaking immediately, and 88.87 and 89.14 per cent. diethylbarbituric acid in Medinal. The present operator found by conducting consecutive extractions, 85.42 per cent. diethylbarbituric acid in Veronal-Sodium and 85.92 per cent. in Medinal, which results are considerably lower than those of Puckner and Hilpert.

(*g*) 1.0000 gm. of Barbital-Sodium was placed in a separatory funnel and dissolved in 12 c.c. water. Two drops methyl orange T. S. and 0.5 c.c. of concentrated sulphuric acid were added at 12 : 30 p. m. Saturday. Twenty-five c.c. of ether were added and shaken well. The aqueous solution was acid. The separator and contents were allowed to stand until 10 a. m. Monday, when they were again shaken. The aqueous solution was drawn off in a second separatory funnel, 15 c.c. of ether added, and, after vigorous shaking, the aqueous solution was transferred to a third separatory funnel; the ether solution was transferred to the first funnel, using 5 c.c. of ether in washing the second separatory funnel. For a third time the aqueous acid solution was extracted with ether (15 c.c.) and the ether (with the 5 c.c. used for washing) was transferred to the first funnel. To the total ether extracts, 15 c.c. of water were added, the whole shaken and the aqueous solution discarded. The ether was evaporated in a tared half-beaker (after washing separatory funnel with two 5 c.c. portions of ether) on a low temperature hot plate in a current of air, and dried at from 90 to 100 C. The yield of diethylbarbituric acid was 84.89 per cent.

(*h*) 1.0000 gm. carried out the same as "g," except that 1 c.c. of concentrated hydrochloric acid was added instead of sulphuric acid, yielded 84.73 per cent. diethylbarbituric acid. It seems that the kind of acid used makes no difference.

Melting Point.—In all cases the melting point of the barbital extracted was found to be from 188 to 189 C. Puckner and Hilpert report 182 to 184 C.

TABLE SHOWING EXTRACTION OF DIETHYLBARBITURIC ACID

	Length of Time	Per Cent Diethylbarbituric Acid
a	Immediately	[illegible]
a-1	[illegible] hour	[illegible]
b	Immediately	[illegible]
c	1½ hours	[illegible]
d	4 hours	[illegible]
e	4 hours	[illegible]
f	4 hours	83.31
g	45½ hours	84.89
h	45½ hours	84.73
Veronal-Sodium	Immediately	85.42
Medinal	Immediately	85.92
Theory		89.33
Veronal-Sodium (Puckner and Hilpert)		89.01 (average)
Medinal (Puckner and Hilpert)		89.95 (average)

It may be that in preparing the sodium salt of diethylbarbituric acid the ring opens up, forming a compound which is not so easily affected by dilute mineral acids. The Laboratory is awaiting with interest the manufacture of this product by other concerns in order to investigate further this interesting discrepancy.

BENZYL ALCOHOL

Benzyl Alcohol, phenmethylol, or phenyl carbinol, $C_6H_5CH_2OH$ has come into prominence as a local anesthetic through the work of Macht.[1] It was proposed for inclusion in New and Nonofficial Remedies by Hynson, Westcott & Dunning, Baltimore, Md. This firm also submitted ampules containing a solution stated to contain, respectively, 1 per cent., 2 per cent. and 4 per cent. by weight of the product in physiologic sodium chlorid solution.

It is stated in the literature that benzyl alcohol occurs as an ester in tolu and other balsams. It is described as a colorless liquid with a faint aromatic odor and a sharp burning taste, soluble in water, 1 c.c. in 25 c.c., and miscible in all proportions with alcohol, ether and chloroform. Its boiling point and specific gravity are variously given. Milliken[2] gives the boiling point at 204.7 C., Schmidt[3] as 206, Richter[4] 206, Beilstein[5] 205.3, and Meyer and Jacobson[6] 204. Milliken gives the specific gravity as 1.043 at 20/4, Schmidt[3] 1.051 at 14 C., Richter[4] 1.062 at 0 C., Beilstein[5] 1.05 at 15/15 and 1.044 at 25/25, and Meyer and Jacobson[6] 1.043 at 19.8 C. It is further stated that it is easily oxidized to benzaldehyd or benzoic acid.

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[1] Macht: J. Pharmacol. and Exper. Therap. April, 1918, p. 263.

[2] Milliken: The Identification of Pure Organic Compounds, Ed. 1, p. 165.

[3] Schmidt: Pharmaceutische Chemie, Ed. 5, p. 1123.

[4] Richter: Organische Chemie, Ed. 12, 1913, p. 236.

[5] Beilstein: Erganz, Handbuch der Organischen Chem. 2: 636.

The sample submitted was found to agree in general as to color, odor, etc., with the foregoing statements. While the solubility was not accurately determined, it seemed to be abount 1 c.c. in 25 c.c. It boiled at from 201 to 206 C., only a very small portion remaining at 206. Its specific gravity at 15/15 was found to be 1.0443 and at 25/25, 1.0372.

It produced a sensation of numbness when placed on the tongue. Simply warming with potassium permanganate was sufficient to give an odor of benzaldehyd, and on heating, benzoic acid was easily obtained.

In conformity with the statements in the literature and the laboratory findings, together with information furnished by Hynson, Westcott & Dunning, and Fritsche Brothers, the following description of benzyl alcohol was prepared:

> **Benzyl Alcohol.**—Phenmethol.—$C_6H_5CH_2OH$.—An aromatic alcohol occurring as an ester in tolu and other balsams, produced synthetically.
>
> Benzyl alcohol is a colorless liquid with a faint aromatic odor, and a sharp burning taste. When placed on the tongue it produces numbness, even in very small quantities. It is soluble, 1 c.c. in 25 c.c. water, and miscible in all proportions with alcohol, ether and chloroform.
>
> Benzyl alcohol boils without decomposition between 200 and 206 C. When ignited it burns with a smoky flame
>
> It has a specific gravity of from 1.040 to 1.050 at 15 C., and 1.032 to 1.042 at 25 C.
>
> Benzyl alcohol is neutral to litmus. If 2 or 3 drops are added to a strong solution of potassium permanganate acidulated with sulphuric acid, rapid oxidation takes place and the odor of benzaldehyd is plainly evident. On heating the mixture further oxidation takes place, and then by adding dilute sulphuric acid and decolorizing the mixture with hydrogen dioxid, benzoic acid may be obtained by extracting with ether.
>
> Wind the end of a copper wire to a spiral about one-fourth inch in diameter and length, hold this spiral in a nonluminous flame until no green coloration is imparted to the latter. Fill the spiral with a few drops of benzyl alcohol and let these burn off outside the flame. Pace the nonluminous flame against a dark background and hold the

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6. Meyer and Jacobson: Organische Chemie, 1902, p. 466.

loop in the right or left margin of the flame. Not even a transient green coloration should be imparted to the latter.

If 5 c.c. are shaken with 5 c.c. sodium hydroxid solution (5 per cent.) and allowed to stand one hour, no yellow color should appear in the aqueous layer (aldehyd).

One volume of benzyl alcohol should dissolve in 1.5 volumes of 50 per cent. alcohol.

Ten c.c. of benzyl alcohol should leave no weighable residue on evaporation and heating until all carbon is burned away.

ECKMAN'S CALCERBS

(Reprinted from The Journal A. M. A., August 10, 1918, p. 486)

"Eckman's Calcerbs" is put out by the same concern as that which exploits "Eckman's Alterative" and is advertised for the same conditions. "Eckman's Alterative," as some of our readers will remember, was an alleged consumption cure which the A. M. A. chemists found to be essentially a mixture of alcohol, calcium chlorid and cloves, and which was sold under such claims as:

> "A medicine made for the cure of tuberculosis. It has cured this disease again and again."
>
> "Cures have been effected . . . . where no intelligent care was taken of the patient, where money was scarce; good food and good cooking unusual."

"Calcerbs" are not frankly sold as a "cure for consumption"; yet as an appeal to the consumptive "Calcerbs for weak lungs" is, doubtless, just as alluring and just as potentially dangerous.

> "If taken in time this calcium compound lessens the risk of chronic throat or lung trouble."
>
> "All the remedial and tonic qualities are combined in this calcium compound."

The purchaser of Calcerbs learns, from the leaflet that accompanies the preparation, that it is for the treatment of "Coughs and Colds, Asthmatic, Catarrhal and Pulmonary Troubles, Weak Lungs, and as a Tonic." One page of the leaflet consists of what purport to be "Some Interesting Comments on Calcium (Lime) Treatment." The "comments" are quotations from various medical journals regarding the therapeutic value of calcium salts. Of course no comments of an unfavorable character are quoted.

Because of the number of inquiries regarding Calcerbs the Association's chemical laboratory analyzed this product.

LABORATORY REPORT ON CALCERBS

"Three original boxes of 'Calcerbs' were purchased on the open market by the Chemical Laboratory. Within the box of tin, sealed by means of adhesive tape, was a waxed-paper bag, containing forty white-coated tablets. The average weight of each tablet was 0.83 gm. (12.9 grains). Test indicated that the tablets contained approximately 20 per cent. of calcium chlorid, the hygroscopicity of which explains the use of a tightly protected package in order to exclude moisture. The tablets were also found to contain calcium carbonate, an emodin-bearing (laxative) drug such as aloin, with sugar and a flavoring of cloves. No iodids, alkaloids or heavy metals were found."

In summing up its article, THE JOURNAL commented:

It is not necessary to tell physicians that "Calcerbs" are just as impotent to cure tuberculosis as is "Eckman's Alterative." As THE JOURNAL has so many times said, the fundamental viciousness of "consumption cures" lies not so much in the valuelessness of their composition as in the fact that their advertisement leads sufferers to abandon or ignore the hygienic and dietetic measures which hold the only hope. That some physicians have recommended calcium salts in pulmonary tuberculosis, based on the unproved supposition that consumption is due to lime deficiency, is no excuse for a "patent medicine" concern putting out calcium chlorid either in liquid or tablet form under thinly veiled claims that will lead the public to infer that the preparations will cure consumption.

COLLO-IODE

At the request of the referee of the Council on Pharmacy and Chemistry in charge of iodin preparations, the Laboratory examined specimens of Collo-Iode Drops and Collo-Iode Injectable, manufactured by H. Dubois, manufacturing chemist, Paris, France, and submitted to the Council by David B. Levy, Inc., 96 Warren Street, New York City.

The specimen of Collo-Iode Drops was a liquid contained in a bottle with a special dropping arrangement, and is described as "a colloidal vegetable-iodine combination," which results "from the molecular fixation of iodin on a vegetable colloid extracted from gluten."

The specimen of Colo-Iode Injectable consisted of 1 c.c. ampules containing a liquid which is said to be "produced by molecular fixation on fat colloids; it is a very stable oily solution." The label on the trade package of Collo-Iode Drops states that "20 drops of DuBois' Collo-Iode contains ¾ grain of iodine in combination with 3 grains of vegetable albumin." The circular which accompanies the bottle states that "20 drops of DuBois's Collo Iode are equivalent to 15 grains of iodide." In a letter the manufacturer states that "Thirty grammes Collo-Iode drops contain one grain of iodine," while in a proposed new label, it is stated that "30 drops of DuBois's Collo-Iode contain 1 grain of iodine."

Collo-Iode Drops consist of a dark brown liquid, acid in reaction and with a benzaldehyd-like odor. The specific gravity was found to be 1.1182 at 15.6 C. It was miscible with water in all proportions. Qualitative tests readily demonstrated the presence of sugar, chlorid and iodid. Free iodin was not present. That the iodin present in Collo-Iode exists as an iodid or iodin compound readily yielding iodid was shown by its response to the tests for iodid. Further confirmation of this fact was demonstrated by the complete precipitation of the iodin on the addition of silver nitrate solution to an aqeuous solution of the product. Twenty drops of Collo-Iode Drops were found to contain 0.47 grain of iodin, instead of 0.75 grain, as claimed on the label of the container. The amount of iodin in Collo-Iode Drops was found to be 4.27 per cent. by weight. Using the same basis for calculation, 30 drops would contain 0.75 grain of iodin rather than 1 grain, as claimed by the manufacturer in a letter dated Dec. 3, 1917. In the circular accompanying the bottle appears the vague expression "20 drops of DuBois's Collo-Iode are equivalent to 15 grains of iodide." If the word "iodide" is interpreted as meaning "a colloidal vegetable iodine combination," the conclusion would be drawn that 75 per cent. of the product consists of an iodized protein. However, if the word "iodide" is interpreted as meaning iodin, potassium iodid or sodium iodid, the claimed amount would be over 100 per cent.

From the examination of Collo-Iode Drops the conclusion is drawn that the product consists essentially of an aqueous solution of an iodid or iodin compound which responds readily to all tests for iodid. Hence, as far as therapeutic use is concerned, the compound can be considered an iodid.

Collo-Iode Injectable was found to consist of a light brown oily liquid with an odor suggestive of cineol. The specific gravity was found to be 1.1855 at 15.6 C. Free iodin was not present. Quantitative determination showed the preparation to contain 26.55 per cent. of iodin. On steam distillation a portion of the product was found to volatilize, leaving in the distilling flask 82 per cent. of a nonvolatile constituent which consisted of an iodized fatty oil. From a physical examination, the volatile constituent was found to closely resemble cineol.

As the names Collo-Iode Drops and Collo-Iode Injectable have such similarity, one would be led to conclude that the products were essentially similar in character, which, according to the chemical examination, is not the case.

DETAILS OF ANALYSIS

Collo-Iode Drops.—

1. *Total Iodin.*—(Kendall's Method, *J. Am. Chem. Soc.*, 1912, p. 894.)

(*a*) 0.7076 gm. on fusion with alkali, oxidation of the iodid to iodate by means of sodium hypochlorite, absorption of the chlorin (Cl^{+}) by phenol liberation of iodin by the addition of iodid and subsequent titration of the iodin with tenth-normal sodium thiosuphate solution (factor 0.9505) took 2.5 c.c. thiosulphate solution, equivalent to 0.0298 gm. iodin, or 4.21 per cent.

(*b*) 0.8485 gm. took 3.05 c.c. sodium thiosulphate solution, equivalent to 0.0368 gm. iodin, or 4.33 per cent.

Collo-Iode Injectable.—

1. *Free Iodin.*—Free iodin could not be detected by the following method: 1 c.c. of the product was dissolved in 10 c.c. of chloroform and shaken with potassium iodid solution. No blue color was produced on the addition of starch solution.

2. *Total Iodin.*—Total iodin in Collo-Iode Injectable was determined in the same manner as the total iodin in the "drops" (Kendall's Method, *J. Am. Chem. Soc.*, 1912, p. 894.)

(*a*) 0.2899 gm. of the product required 6.4 c.c. of tenth-normal sodium thiosulphate solution (factor 0.9505), equivalent to 0.0774 gm. of iodin, or 26.7 per cent.

(*b*) 0.3416 gm. required 7.5 c.c. of tenth-normal sodium thiosulphate solution, equivalent to 0.0901 gm. of iodin, or 26.4 per cent.

The label on the trade package states that the product contains 30 centigrams of iodin per cubic centimeter. Calculating from the specific gravity the amount of iodin present would be 25.2 per cent. A letter from the manufacturer to the Council stated that Collo-Iode Injectable contained 27.5 per cent. of iodin.

3. *Fixed and Volatile Oils.*—7.45 gm. of Collo-Iode Injectable were subjected to steam distillation. A volatile oil closely resembling cineol was obtained, but owing to the small amount of volatile material this constituent could not be positively identified.

The fatty oil remaining in the flask was carefully separated from the water present, dried with calcium chlorid, filtered off and weighed; 6.13 gm. were thus obtained, corresponding to 82 per cent. A portion of the fixed oil was found to be completely saponifiable with alcoholic potassium hydroxid, thus indicating that it consisted of a fatty oil. The saponified portion readily gave a test for iodin, showing that it was an iodized fatty oil.

From the foregoing it was concluded that Collo-Iode Injectable consisted of a mixture of an iodized fatty oil and a volatile oil (probably cineol).

The preceding examinations indicate that Collo-Iode Drops and Colloidine (submitted by the same manufacturer in 1915) are essentially the same, with the exception that Colloidine was marketed in tablet rather than liquid form. Colloidine was found to contain about ¼ grain of iodin per tablet, and the largest daily dose was 15 tablets, corresponding to 4.5 grains of potassium iodid, or 3.75 grains of sodium iodid (Rep. A. M. A. Chem. Lab. **8**: p. 127).

The small dose of iodid thus administered was considered as accounting for the declared absence of iodism after administration. Likewise the absence of symptoms of iodism after the use of Collo-Iode can be accounted for, the smallest daily dose being 10 "drops," corresponding to 0.31 grain of potassium iodid, or 0.27 grain of sodium iodid, and the largest dose being 100 "drops," corresponding to 3.1 grains of potassium iodid. Inasmuch as both products are exponents of the same idea of medication, it is to be noted that the iodid dosage since 1915 has undergone a considerable decrease.

D-O-D SPECIFIC NO. 3

One box (content 6 ounces) of "D-O-D Specific No. 3," manufactured by the C. Nelson Smith Co., Milwaukee, was submitted to the Chemical Laboratory for examination. Some of the claims made for the products are:

> "Disinfectant and De-Odorant. Destroys all offensive smells, leaves no odor. Especially recommended for hospitals and schools.

> "Non-Poisonous Remedy for Diphtheria, Sore Throat, Stomach and Bowel Troubles.
>
> "Home Remedy for gangrene, aching, tired, sore, sweaty and bad smelling feet, barber's itch, burns, scalds, cholera morbus, colic, chilblains, sores, eczema, hives, rashes, and other skin diseases."

The product was a grayish powder with purple crystals here and there, showing it not to be well mixed.

Qualitative tests indicated sodium bicarbonate and potassium permanganate No heavy metals were found. Borate, phosphate or chlorid was not found to be present. Titration of a portion of the specimen indicated the presence of 2.98 per cent. potassium permanganate. The examination indicates that "D-O-D Specific No. 3" is essentially a mixture of sodium bicarbonate with 3 per cent. potassium permanganate.

In view of the foregoing, a discussion of the extravagant claims is unnecessary. The product is not worth $1.50 for 6 ounces—the price at which it is sold.

EMETIN BISMUTH IODID

By William Rabak, Ph.G., B.S.

In view of favorable reports with regard to the use of emetin bismuth iodid as a means of administering emetin in the treatment of amebic dysentery, the Council on Pharmacy and Chemistry decided to consider this drug with a view of its admission to New and Nonofficial Remedies. Two firms, the H. K. Mulford Company and the Abbott Laboratories, having undertaken to manufacture emetin bismuth iodid and having offered to aid in its standardization, the Council submitted to the Laboratory the information and specimens received from these firms and requested the elaboration of standards and tests for the control of the quality of the drug.

Meyer's reagent (mercuric potassium iodid) and Dragendorff's reagent (bismuth potassium iodid) have long been employed in the detection of alkaloids by virtue of the precipitate which is produced when either of them is added to a solution of an alkaloid. Thus, in the case of the detection of emetin, the first forms a yellow precipitate of emetin mercuric iodid and the second an orange-red precipitate of emetin bismuth iodid. Neither of these precipitates was regarded from the therapeutic standpoint until, in 1914, DuMez (*Philippine J. Sc.*, January, 1915, p. 73), suggested emetin bismuth iodid as a compound which might be of value for oral administration in the treatment of entamebiasis. DuMez prepared emetin bismuth iodid by adding Dragendorff's reagent to an acidified solution of emetin hydrochlorid. The resulting emetin bismuth iodid was found to be insoluble in water or water acidulated with hydrochloric acid, which gave basis for the belief that the compound would not be decomposed to any great extent in the stomach, thus lessening its nauseating effect. He found, on analysis of his product, that it consisted of iodin 58.26 per cent., bismuth 12.36 per cent., hydrogen (of hydrogen iodid) 0.3 per cent., and emetin (by difference) 29.08 per cent. These results led him to assign the following formula to emetin bismuth iodid, $(C_{30}H_{40}N_2O_4)(5HI)(BiI_3)$. Further work on the compound led him to conclude that the composition of the compound varied with the concentration of the solutions employed.

The Abbott Laboratories states that: "Emetine Bismuth Iodide is a definite chemical compound having the following formula: $C_{30}H_{42}N_2O_4.24I.2BiI_3$," and that "this salt should contain about twenty-five per cent of emetin alkaloid." They also suggested the following assay:

> "Shake thoroughly about 0.200 gm., with 50 c.c. of 10 per cent. ammonia water. Extract the liberated alkaloid with ether, evaporate and titrate. To the solution after titration add an excess of NaOH and shake out the emetin with ether. Acidify the alkaline liquor, add an excess of ammonia and extract again with ether. The residue after evaporation of the ether should not give a purple color on addition of a drop of sulphomolybdic acid (absence of cephaeline)."

The H. K. Mulford Company stated that the content of anhydrous emetin alkaloid in the bismuth emetin iodid manufactured by it ranged between 27.75 per cent. and 30.0 per cent. The firm suggested a standard placing the emetin content of this compound between 27 per cent. and 30 per cent.

The H. K. Mulford Co. also suggested a standard for the bismuth content and proposed 10 per cent. to 14 per cent. bismuth, or that the salt should be required to contain about 10 per cent. of bismuth.

Both of the firms named suggested certain qualitative tests.

The Mulford Company sent a specimen of emetin bismuth iodid in powder and also packages of cachets of bismuth emetin iodid stated to contain emetin bismuth iodid, 0.13 gm. The Abbott Laboratories submitted to the powder only.

In taking up the elaboration of standards and methods of examination of emetin bismuth iodid, it was the desire to make use of and accept the proposed methods and standards as far as possible. However, the methods actually used and the standards finally adopted are somewhat different from those proposed by the two firms, either because exact details were lacking, or because some revision appeared desirable.

The following assays were carried out:

Assay of Emetin Bismuth Iodid

To about 0.5 gm. of emetin bismuth iodid in a glass stoppered flask, add 10 c.c. of water and 3 c.c. of ammonia water. Shake and allow to stand ten minutes. Add 50 c.c. of ether to the flask, and shake every ten minutes during two hours. Decant 25 c.c. of the ethereal layer into a 25 c.c. graduated flask. Filter this through a pledget of cotton into a tared beaker. Wash the flask and filter with ether. Evaporate the ether, dry at 100 C. and weigh (anhydrous emetin). The weight of alkaloid found multiplied by 2 equals the weight of total alkaloid contained in the emetin bismuth iodid. The weights of emetin obtained above were checked by titration.

Bismuth was estimated by the following method: Dissolve about 0.5 gm. emetin bismuth iodid in 30 c.c. of hydrochloric acid with the aid of heat. Dilute to 250 c.c. and heat to below the boiling point. Add ammonia water until a slight turbidity appears. Add hydrochloric acid drop by drop until the solution just becomes clear. Heat to boiling, add 50 c.c. of a 10 per cent. ammonium phosphate solution and boil for several minutes. Let stand for one-half hour. Filter off on tared Gooch crucible, which has been ignited for one hour in a nickel crucible before being weighed. Wash with hot water, dry, and ignite in a nickel crucible to constant weight. The weight of bismuth phosphate ($BiPO_4$) multiplied by 0.6863 equals the weight of bismuth.

The test for cephaeline was carried out on the residue of emetin (from emetin estimation) employing the method of the U. S. P. After the alkaloid has been titrated as described, an excess of sodium hydroxid solution is added and the emetin shaken out with ether. The remaining alkaline liquor is acidified, an excess of ammonium hydroxid added and again extracted with ether. The residue, after evaporation of the ether, should not give a purple color on the addition of sulphomolybdic acid.

TABLE 1.—ASSAYS OF EMETIN AND BISMUTH

	Abbott's Specimen	Mulford's Specimen
Emetin I	29.9 per cent.	27.9 per cent.
Emetin II	29.6 per cent.	27.16 per cent.
Bismuth I	16.98 per cent.	17.41 per cent.
Bismuth II	16.49 per cent.	17.61 per cent.

By the titrametric method numbers II (in the tabulation) were found to contain 21.3 per cent. (Mulford) and 23.37 per cent. (Abbott) of emetin.[1] Emetine Bismuth Iodide-Abbott gave a very slight test for cephaeline.

ASSAY OF CACHETS OF BISMUTH EMETINE IODIDE-MULFORD

Determinations of emetin and bismuth were made on the contents of the Cachets of Bismuth Emetine Iodide-Mulford as follows:

The emetin was determined as described under emetin bismuth iodid. The bismuth was determined as follows: The flask, containing the residue from the emetin determination, was placed on the water bath and the remaining ether allowed to evaporate. The aqueous liquid and precipitate were transferred to a beaker rinsing the flask with a few cubic centimeters of concentrated hydrochloric acid. Thirty c.c. of hydrochloric acid U. S. P. were added and boiled to complete the solution. The solution was diluted to about 300 c.c., filtered and the bismuth phosphate precipitated in the usual manner.

TABLE 2.—ASSAY OF MULFORD'S PREPARATION

	Emetin by Weight	Emetin by Titration	Bismuth
I	22.85 per cent.	11.9 per cent.	17.56
II	22.17 per cent.	16.06 per cent.	16.86

Owing to the fact that the duplicate determinations of emetin in the cachets failed to check, two more determinations were made. In these determinations the ether was allowed to evaporate spontaneously and the residue dried over sulphuric acid, weighed, and after the addition of fiftieth-normal sulphuric acid, titrated with fiftieth-normal alkali.[2] One c.c. fiftieth-normal H_2SO_4 is equivalent to 0.0048 gm. of emetin.

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[1] The H. K. Mulford Company explained that the extremely low results obtained by titration was very likely due to an alteration of the alkaloid by the heat and reagents used in manufacturing the product. The Abbott Laboratories made no comment on this point. It is also possible that during the process of rapid evaporation, hydrolytic or other changes altered the character of the base.

TABLE 3.—SECOND ASSAY OF MULFORD'S PREPARATION

	Weight of Emetin Bismuth Iodid	Weight of Emetin	Per Cent. of Emetin by Weight	Per Cent. by Titration
I	0.5835	0.134	22.98	18.26
II	0.6748	0.1532	22.71	17.63

To check up the bismuth determined by the phosphate method, two determinations were made by the bismuth oxid method (Rep. A. M. A. Chem. Lab., 1911, p. 18). In one case 0.5229 gm. of emetin bismuth iodid yielded 0.1052 gm. of Bi_2O_3, corresponding to 18.02 per cent. of bismuth. In the other case 0.5835 gm. of emetin bismuth iodid yielded 0.1031 gm. of Bi_2O_3, or 17.66 per cent. of bismuth. An average of the bismuth determinations made by the phosphate method on the cachets was found to be 17.21 per cent. The average of the determinations by the oxid method is 17.84 per cent., indicating that the phosphate method in all probability yielded reliable results.

The preceding would appear to warrant the recommendation that in the establishment of standards for emetin bismuth iodid the amount of emetin be determined by titration rather than by weight, and the bismuth be determined on the residues left after the determination of emetin.

In practically all instances emetin bismuth iodid produces nausea and purging. As Dr. DuMez, in a private communication, suggested that this might be due to occluded emetin not removed by washing the precipitate, experiments to determine this were made in accordance with the suggestions of the referee of the Council in charge of the product.

EFFECT OF SOLVENTS ON EMETIN BISMUTH IODID

A. Solubility of Emetin Bismuth Iodid.—Samples of 0.1 gm. were shaken with 10 c.c. of solvent for two minutes, allowed to stand in contact with the solvent forty-five minutes, filtered, and the filtrate treated with 3 drops of mercuric-potassium-iodid solution (the alkaline filtrates being first acidulated).

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[2] It will be noted that the volumetric and gravimetric results agree more closely when the solvent is allowed to evaporate at room temperature and the residue dried over sulphuric acid. This is in agreement with the theory that the character of the base is altered by rapid evaporation and drying at an elevated temperature.

TABLE 4.—SOLUBILITY IN VARIOUS SOLVENTS

Solvents	Appearance (Mulford's Specimen)	Appearance (Abbott's Specimen)
1. 0.5 per cent. HCl.	Color of solution yellow; turbidity and curdy precipitate	Solution yellow; turbidity and curdy precipitate
2. 1 per cent. $NaHCO_3$	Color of solution yellow; considerable more precipitate than in (1)	Solution yellow; volume of precipitate much greater than in (1)
3. 1 per cent. $NaHCO_3$ 0.04 per cent. Bile salts	Color yellow; volume of precipitate as (2)	Solution yellow; volume of precipitate same as (2)
4. Distilled water ...	Color solution bright amber; turbidity and twice amount of precipitate under (1)	Solution very bright amber; turbidity and more curdy precipitate than (1)

CONCLUSIONS

The product is slightly more soluble in distilled water than in 0.5 per cent. hydrochloric acid. In an alkaline medium (that is, 1 per cent. $NaHCO_3$) and in an alkaline medium and bile salts, it is much more soluble than in 0.5 hydrochloric acid. This solubility is evidently due partly to decomposition into its constituents, as shown by the following experiments:

TABLE 5.—EFFECT OF SOLVENT

	Mulford's Specimen		Abbott's Specimen	
1 gm. Emetine Bismuth Iodide with	0.1 gm. Emetine Bismuth Iodide with 0.5 per cent. HCl	0.1 gm. Emetine Bismuth Iodide with distilled water	0.1 gm. Emetine Bismuth Iodide with 0.5 per cent. HCl	0.1 gm. Emetine Bismuth Iodide with distilled water
Stood ¾ hours with 10 c.c.	Turbidity and curdy precipitate	Turbidity and twice curdy precipitate of 0.5 per cent. HCl	Turbidity and curdy precipitate	Turbidity and more curdy precipitate than in 0.5 per cent. HCl
Residue washed with 90 c.c.	Less curdy precipitate than above	Less curdy precipitate than above	Curdy precipitate less than above	Precipitate less than above, but greater than in 0.5 per cent. HCl
After washing stood over night with 10 c.c.	⅓ as much precipitate as in (1)	⅓ as much precipitate as in (1)	Very faint turbidity	Considerable turbidity and some precipitate

B. Is the Acid and Water Soluble Emetin Present as an Impurity, or Is It Dissolved or Split Off by the Solvent?—The undissolved emetin bismuth iodid under A-1 and A-4 was washed on a filter with 90 c.c. of their respective solvents (that is, 0.5 per cent. HCl in (1) and water in (4)), and 10 c.c. of each filtrate examined as in A by the addition of 3 drops of mercuric-potassium-iodid solution. The undissolved substance on the filter was left over night with 10 c.c. of its respective solvent and then filtered and tested as in A.

The foregoing experiments show that emetin is split off by the action of the solvent.

The control experiments on the solubility tests were conducted as follows: 0.1 gm. emetin bismuth iodid was added to 100 c.c. of distilled water in a glass stoppered graduate. It was shaken for one minute and 5 c.c. decanted through a filter and this tested by addition of 2 drops of mercuric-potassium-iodid. The graduate was stoppered and again shaken for one minute and allowed to stand five minutes; 5 c.c. decanted through filter and tested with mercuric-potassium-iodid. The graduate was again shaken for one minute, allowed to stand fifteen minutes, etc., twenty-five minutes and four hours. Table 6 shows the results obtained.

TABLE 6.—RESULTS OF CONTROL TESTS

Time	Appearance (Mulford's Specimen)	Appearance (Abbott's Specimen)
1. 1 Minute......	Quite turbid and small amount of precipitate	Turbid but not as much so as Mulford's specimen
2. 5 minutes.....	Turbidity and precipitate increased	Turbidity increased and small amount of precipitate
3. 15 minutes....	Turbidity and precipitate same as (2)	Turbidity increased same as (2)
4. 25 minutes....	Turbidity and precipitate more than (3)	Turbidity greater than in (3)
5. 4 hours.......	Considerable curdy precipitate	Considerable curdy precipitate

Table 6 indicates that a test for emetin in the product does not necessarily mean that free emetin is present, but that emetin bismuth iodid is decomposed slowly in contact with water.

As the result of the work done, and after submission of the results to the manufacturer for comments, a descriptive monograph was designed to limit the amount of uncombined emetin as well as to control the amount of combined emetin and bismuth. The monograph is as follows:

EMETIN BISMUTH IODID. — Emetinae Bismutho-Iodium.—Emetin Bismuthous Iodid.—Bismuth Emetin Iodid. —A complex iodid of emetin and bismuth, containing from 17 to 23 per cent. of anhydrous emetin and from 15 to 20 per cent. bismuth.

Emetin bismuth iodid is an odorless, orange-red powder having a slightly bitter taste.

It is but slightly soluble (with decomposition and liberation of emetin) in water, and dilute acids. It is decomposed by alkaline liquids and by strong acids.

Shake 0.1 gm. of emetin bismuth iodid with 10 c.c. of tenth-normal hydrochloric acid volumetric solution during fifteen minutes. Filter and dilute 1 c.c. of the filtrate to 100 c.c. To a 5 c.c. portion add 1 drop of mercuric potassium iodid test solution, shake and allow to stand one minute. No distinct milkiness or turbidity should appear.

When assayed by the following method, emetin bismuth iodid contains from 17 to 23 per cent. of anhydrous emetin and from 15 to 20 per cent. of bismuth.

To about 0.5 gm., accurately weighed, of emetin bismuth iodid in a glass stoppered flask add 10 c.c. of water and 3 c.c. of ammonia water, shake and allow to stand ten minutes. Add 50 c.c. of ether to the flask, shake for ten minutes and then shake every ten minutes during two hours. Decant 25 c.c. of the ethereal layer into a 25 c.c. graduated flask. Filter this through a pledget of cotton into a small beaker. Wash the flask and filter with ether. Allow the ether to evaporate spontaneously and dry over sulphuric acid. Take up the alkaloid with fiftieth-normal sulphuric acid volumetric solution and titrate back with fiftieth-normal sodium hydroxid volumetric solution using cochineal as an indicator. Each of fiftieth-normal sulphuric acid volumetric solution consumed is equivalent to 0.0048 gm. of anhydrous emetin.

Place the flask, containing the residue from the emetin determination, upon the water bath and allow the remaining ether to evaporate. Transfer the aqueous liquid and precipitate to a beaker rinsing the flask with a few c.c. of concentrated hydrochloric acid. Add about 30 c.c. of concentrated hydrochloric acid to the beaker and boil. Dilute to about 300 c.c., again heat to boiling and filter. Add ammonia water until a slight turbidity appears. Add hydrochloric acid drop by drop until the solution just becomes clear. Heat to boiling, add 50 c.c. of 10 per cent. ammonium phosphate solution and boil for several minutes. Let stand for one-half hour. Transfer the precipitate to a tared Gooch crucible, which has been strongly heated for one hour in a nickel crucible before being weighed. Wash with hot water, dry and heat in a nickel crucible to constant weight. Each gm. of bismuth phosphate ($BiPO_4$) corresponds to 0.6863 gm. of bismuth.

EXAMINATION OF AMERICAN-MADE PHENYLCINCHONINIC ACID

Phenylcinchoninic acid was introduced in medicine under the proprietary name "Atophan," by Schering & Glatz, New York City, whose firm before the war was the American agent for the German manufacturers, Chemische Fabric auf Actien von E. Schering, Berlin, Germany. Phenylcinchoninic acid (2=phenyl=4=quinolin carboxyllic acid) was first described by Doebner and Gieseke[1] in 1887, who prepared it by warming together pyroracemic acid, benzaldehyd and anilin in alcoholic solution; it has the structural formula

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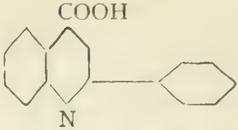
1. Ann. d. Chem. (Liebig's) **240:** 291, 1887.



In 1913 the German house of Schering was made the assignee of Patent 1,045,759 granted by the United States Government for the manufacture of phenylcinchoninic acid; at about the same time the product was admitted to the U. S. Pharmacopeia IX.

According to N. N. R., phenylcinchoninic acid stimulates the kidneys so as to increase the amount of urine and have a selective action on the excretion of uric acid, which is increased in greater ratio than the increase in amount of urine. It is said to be useful in acute gout; it relieves pain in this disease, acting more promptly than colchicum and without undesirable by-effects.

Some time after the beginning of the European belligerency the proprietary "Atophan" became scarce in America. Over a year ago, however, Schering & Glatz, Inc., New York, placed American-made Atophan on the market and submitted it to the Council on Pharmacy and Chemistry. Later other firms began to manufacture the products and also submit them. In making the examinations for the Council, the Laboratory was practically confined, by virtue of the Food and Drugs Law, to limit its requirements of purity to those of the Pharmacopeia. During the time it was investigating these products the Federal Trade Commission received applications for licenses to manufacture the drug under the patent just referred to, so that all together the laboratory had a number of specimens to examine.

Practically, the only tests of purity which could be made under the provisions of the U. S. P. description were melting point, ash and solubility.

According to the U. S. Pharmacopeia, the melting point is "about 210 C." In New and Nonofficial Remedies, 1918, it is explained that Atophan "complies with the standards for phenylcinchoninic acid U. S. P., but melts between 208 and 212 C." The U. S. Pharmacopeia requires that no weighable ash remains on incinerating about 0.5 gm. phenylcinchoninic acid.

The melting point determinations were conducted according to the method of the U. S. P. IX.

The ash determinations were conducted by the usual method, which consists in the careful ignition of about 1 gm of the substance in a crucible, cooling in a desiccator and weighing when cold.

Considerable variations, especially in melting points, were found, as can be seen from the accompanying Table 1.

TABLE 1.—MELTING POINTS

Product No.	Manufacturers	Melting Point, Centigrade	Ash, Per Cent
1.	Abbott Laboratories, Chicago	208.5-210.5	0.05
2.	Abbott Laboratories, Chicago	212 -213	0.05
1.	Calco Chem. Co., Bound Brook	209 -210.5	0.07
1.	Morgenstern, New York	204.5-207.5	2.8
2.	Morgenstern, New York	209.5-211.5	none
1.	Schering and Glatz, New York	206 -208	none
2.	Schering and Glatz, New York	209 -211	none
3.	Schering and Glatz, New York	208.5-210	0.17
4.	Schering and Glatz, New York	(1) 208.5-210	0.2
		(2) 208.5-209.5	0.3
		(3) 208.5-210	0.25
1.	Wm. H. Sweet and Co., Columbus	204.208	none
2.	Wm. H. Sweet and Co., Columbus	209.5-211.5	0.04
1.	German specimen from Schering and Glatz	210.212	none

Solubility of Phenylcinchoninic Acid.—As methods of determining impurities, or estimating the degree of purity of phenylcinchoninic acid were not described in the U. S. Pharmacopeia, it was decided to try extraction methods.[2]

This in turn led to the question of solubilities. The U. S. Pharmacopeia gives the solubility of phenylcinchoninic acid only in general terms; hence it was deemed advisable to determine its solubilities and describe them in more definite terms.

The sample of phenylcinchoninic acid employed to determine the solubility was obtained by repeated recrystallization from alcohol of a commercial specimen. Solubilities were determined in water, alcohol 95 per cent., alcohol 48.5 per cent.,[3] chloroform and ethyl acetate.[4]

Complete saturation of the solvent was attained according to the following (U. S. P. IX) method:

> A test tube of medium size was fastened upright in a waterbath maintained at a temperature of 25 degrees with a range of 0.2 degrees. The solvent and excess solids were

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[2] Attempts were made to make salts of phenylcinchoninic acid with metals such as *copper, mercury, barium* and *calcium;* also the chloroplatinic acid or per-iodid addition products. However, reliable quantitative results could not be obtained.

[3] This corresponds to "Diluted Alcohol, U. S. P."

[4] The ethyl acetate was Merck's product (redistilled) stated to contain 81.6 per cent. of ethyl acetate, 10 per cent. alcohol and alcohol derivatives.

placed in the tube and stirred by means of a motor-driven rotating glass spiral. After complete saturation the solution was analyzed according to the method of Seidell[5] as follows:

At the end of the period of rotation the spiral was removed and the undissolved material allowed to settle to the bottom of the tube. The tube was then placed in a beaker filled with water taken from the constant temperature bath and immediately syphoned with the aid of a suction pump through a plug of cotton into a 25 c.c. pycnometer. This was accomplished by employing a closed glass cylinder large enough to contain the pycnometer. The syphon tube passed through a stopper in the top of the cylinder directly into the mouth of the pycnometer. Suction was applied through another opening in the glass cylinder. After filling, the pycnometer was immediately weighed. The saturated solution was then transferred to a weighing bottle, the solvent evaporated and the residue weighed.

The data obtained for the solubility of phenylcinchoninic acid were as shown in Table 2.

TABLE 2.—SOLUBILITY OF PHENYLCINCHONINIC ACID

Solvent	Specific Gravity of Solvent at 25 C.	Gm. per 100 Gm. of Sat. Solution	Solubility Parts by Weight
Distilled water	0.9991	0.0160	1 in 6216.0
95 per cent. ethyl alcohol	0.8052	0.8343	1 in 119.0
Dilute ethyl alcohol	0.9313	0.0875	1 in 1142.6
Chloroform	1.4760	0.1075	1 in 929.7
Ethyl Acetate	......	1.4151	1 in 70.0

The Abbott Laboratories, Chicago, Ill., have been licensed by the Federal Trade Commissoin to manufacture phenylcinchoninic acid. Other firms, however, have decided to manufacture it without the formality of obtaining a license, evidently considering the German-obtained patent *not* to be valid.

By referring to the table on melting points and ash contents, it will be noted that the production of a better grade of products resulted after the respective firms had submitted samples to the A. M. A. Chemical Laboratory for criticism, and from a chemical standpoint the last products examined were found *not* to be inferior to the German-made "Atophan."

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[5] Seidell, A.: Hyg. Lab. Bull. 67, Public Health and Marine Hospital Service, p. 11.

EXAMINATION OF NOVOCAIN-SUPRARENIN TABLETS "T"

A specimen of Novocain-Suprarenin Tablets "T" was examined for the American Red Cross, at the request of the Council on Pharmacy and Chemistry, to determine if a lot which had been purchased was acceptable.

The label for the tablets contained the following:

12 Tubes Each Containing
20 Novocain-Suprarenin Tablets "T"
For Local Anesthesia
Each Novocain 0.02 gram
Each Suprarenin 0.00002 gram

Procain (novocain) was identified in the tablets by the following tests given in New and Nonofficial Remedies, 1918, p. 33:

1. Precipitation by the usual alkaloidal reagents, such as potassium-mercuric-iodid, picric acid, etc.
2. The precipitation of the free base from aqueous solutions by the addition of sodium hydroxid solution and sodium carbonate solution.

The identity was further substantiated by tests given under novocain in the German Pharmacopeia, Ed. 5, 1910, p. 363. These tests were:

1. A solution of about 0.1 gm. (5 tablets) in 5 c.c. of distilled water, on addition of 2 drops of dilute hydrochloric acid and 2 drops of sodium nitrate solution, produces a scarlet red precipitate in an alkaline betanaphthol solution.
2. If a solution of about 0.1 gm. of novocain in 5 c.c. of distilled water and 3 drops dilute sulphuric acid be mixed with 5 drops potassium permanganate solution, the violet color disappears immediately (distinction from cocain).
3. Silver nitrate solution added to an aqueous solution of the tablets acidified with nitric acid, produces a white precipitate soluble in ammonium hydroxid.

The presence of epinephrin (suprarenin) was indicated by the pink coloration which was produced when an aqueous solution of the tablets was treated with a small amount of manganese dioxid (Seidell: *J. Biol. Chem.* **15**:197).

An attempt to utilize the Pharmacopoeial method for the estimation of the epinephrin in the tablets failed because procain was found to produce a yellow color with manganese dioxid.*

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* Experiments carried out to elaborate a method appear at the end of this article.

Attempts to apply the method of Folin, Cameron and Denis (*J. Biol. Chem.* **13**:477) also failed.

ESTIMATION OF PROCAIN

To determine the amount of procain contained in the tablets a "total alkaloid" estimation was made and the results calculated to procain ($CH_2(C_6H_4.NH_2.COO).CH_2.N(C_2H_5)_2.HCl$), the small amount of epinephrin being negligible in this estimation.

The method employed was suggested by Prof. Torald Sollmann in a personal communication, thus:

> The tablets are dissolved in water, made strongly alkaline with ammonia water and extracted with five or more portions of chloroform. The chloroform is removed from the united extractions by distillation and the residue heated on a steam bath for one hour. This residue is dissolved in approximately hundredth-normal sulphuric acid solution and the excess of acid determined by titration with hundredth-normal sodium hydroxid solution, methyl red being used as indicator. From the volume of acid consumed by the alkaloidal residue the amount of procain present is calculated by the use of a factor established by a similar treatment of known amounts of procain of established identity: 1 c.c. hundredth-normal sulphuric acid solution equaled 0.00295 gm. procain.

Five tablets, weighing 0.0974 gm., when extracted, as detailed, required for the titration 32.6 c.c. acid. This is equivalent to 98.6 per cent. procain.

Five tablets weighing 0.0995 gm. required for the titration 32.9 c.c. hundredth-normal sulphuric acid, equivalent to 95.3 per cent. procain.

The average of the two determinations gives 97.4 per cent. procain. Based on the claimed composition of the tablets and their weight, they should contain 99.4 per cent. procain.

To determine if individual tablets presented an undue variation in weight, the weight of each tablet in a tube of twenty tablets was taken. The weights varied from 0.0167 gm. to 0.0219 gm. The average weight of the tablets was 0.0190 gm. Hence the weight of the lightest tablet was 87.9 per cent. of the average, and weight of the heaviest tablet was 115.2 per cent. of the average. This variation in the weight of individual tablets is not considered excessive in view of the finding for hypodermic morphin sulphate tablets (Rep. A. M. A. Chem. Lab. **6**:10) and the work of L. F. Kebler (*J. Am.*

Pharm. A., 1914, p. 1062), who concluded "In complex, very small and difficult tablets to manufacture, the variation from the declaration may be as great as 15 per cent."

Since, in the acceptance of brands of procain the Council on Pharmacy and Chemistry has considered it a wise precaution to determine their toxicity, Prof. R. A. Hatcher of Cornell University Medical School was asked to estimate the toxicity of these tablets. Dr. Hatcher reported that, "Assuming that each tablet actually contains the amount of novocain indicated, the toxicity compared almost exactly with that of other specimens of novocain and procain previously examined."

In consideration of the preceding, the following report was made to the American Red Cross by the Council on Pharmacy and Chemistry.

The following is the result of the examination of Novocain-Suprarenin Tablets "T" received from you March 26, 1918:

1. According to the label, the tablets are the product of the Farbwerke-Hoechst Co., New York. Each tablet is claimed to contain novocain 0.02 gm. and suprarenin 0.00002 gm.
2. The tablets were found to contain procain (novocain) and epinephrin (suprarenin) as claimed.
3. The toxicity of the procain (novocain) contained in the tablets was no greater than that of an authentic specimen of novocain and of other authentic specimens of procain.
4. The average content per tablet of procain (novocain) agreed closely with the amount claimed for each tablet.
5. The amount of epinephrin (suprarenin) contained in the tablets was not determined.
6. Based on the weight of twenty tablets taken from one tube, the weight of the individual tablets ranged from 15 per cent. below to 15 per cent. above the average weight of the tablets. This variation is not excessive for small tablets.

The preceding work was carried out in the A. M. A. Chemical Laboratory, except that the toxicity of the procain (novocain) was determined in the pharmacologic laboratory of Prof. R. A. Hatcher at Cornell University Medical School.

ESTIMATION OF EPINEPHRIN

An elaboration of Seidell's method was employed. It consists in the addition of manganese dioxid to an aqueous solution of epinephrin, shaking and allowing to stand from thirty minutes to one hour and comparing the color developed with standards of known epinephrin content.

As described in the preceding, the manganese dioxid reagent of Seidell was found to produce a yellow color with procain in aqueous solution of such intensity as to interfere with the delicate pink color formed by the action of manganese dioxid on epinephrin. Hence, in order to imitate as closely as possible the conditions obtained by dissolving one of the tablets in 10 c.c. of water, 200 mg. of procain were added to each tube employed as a standard, together with varying amounts of epinephrin. Color standards were made up as follows: Six tubes of equal diameter were selected and numbered. To each tube was added 200 mg. of procain, 5 mg. of manganese dioxid and amounts of epinephrin varying from 0.005 mg. to 0.03 mg., each differing by 0.005 mg. The tubes were then shaken several times during a period of forty-five minutes and filtered into tubes of equal size. The epinephrin employed was a sample of l-suprarenin synthetic bitartrate obtained from the Farbwerke-Hoechst Company. According to the manufacturers, 1.82 gm. of l-suprarenin bitartrate is equal to 1 gm. of the l-suprarenin base.

In estimating the amount of epinephrin in the product, individual tablets were placed in test tubes which were the same size as those employed in making up the standards, 10 c.c. of water added and shaken until solution was effected. Five mg. of manganese dioxid were then added to each tube, the tubes were shaken, allowed to stand and the contents filtered as above. Color comparisons to the standards were made by viewing the tubes vertically on the surface of white paper.

According to the foregoing method the tablets were found to contain amounts of epinephrin varying from 25 per cent. above to 25 per cent. below the claimed amount. Thus, in a series of determinations, eight tablets were found to contain 75 per cent., six contained 100 per cent. and three 125 per cent. of the claimed content. Since the weight of the tablets had been found to vary from 15 per cent. above to 15 per cent. below the average, the variation in epinephrin content was not considered excessive. The somewhat greater range in epinephrin content found in the preceding is probably due to the limited accuracy of the colorimetric method.

This conclusion is supported by the following experiments carried out to verify the accuracy of the above determinations: Solutions containing varying but unknown quantities of epinephrin (they were made up by a second operator and their contents not disclosed to the first), were placed in test tubes, and after the addition of 200 mg. of procain to each tube, were examined by the first operator, as before. The results indicated that a fluctuation of 25 per cent. above or 25 per cent. below the actual epinephrin content could exist without sufficient change in color to be readily detected by comparison with the standards.

The results were taken as indicating that the specimens of Novocain-Suprarenin Tablets "T" contained the claimed amount of epinephrin. This was confirmed by a report to the Council on Pharmacy and Chemistry, by Torald Sollmann, that by a pharmacologic method the same conclusion had been reached.

In view of the preceding, the Council advised the American Red Cross that while the determinations were not satisfactory, they indicated that the amount of epinephrin (suprarenin) contained in the Novocain-Suprarenin Tables "T" is essentially in accord with the amount claimed.

DETERIORATION OF SODIUM HYPOCHLORITE SOLUTIONS ("Chlorinated Soda" Solutions)

The following note on two hypochlorite solutions is published as a slight addition to the inconclusive available information concerning the rate of deterioration of solutions containing sodium hypochlorite:

Hyclorite.—This is a solution of chlorinated soda, 100 gm of which is said to contain sodium hypochlorite 4.05 gm., sodium chlorid 3.20 gm., calcium hydroxid 0.25 gm., inert ingredients 0.92 gm. It is declared to contain, when placed on the market, not less than 3.85 per cent. of available chlorin, and to deteriorate at the rate of about 12 per cent. per year. In order that the available chlorin content at the time of use may be judged, the date of bottling is stamped on each package. The solution is prepared by decomposing chlorinated lime suspended in water with sodium carbonate and adding to the solution obtained a freshly prepared solution of electrolyzed sodium chlorid. The composition and keeping qualities of hyclorite were reported on by this Laboratory (Ann. Rep. Chem. Lab., A. M. A. **9**: 123, 1916). Hyclorite is fully described in New and Nonofficial Remedies, 1918, p. 153.

To further check the keeping qualities of hyclorite, a specimen received from the manufacturer in June, 1918, and said to have been bottled in April, 1918, was examined in September, 1918. It was found to contain 3.6 per cent. "available chlorin" (equivalent to 3.79 gm. sodium hypochlorite in

100 gm.). This indicated a loss of 6.2 per cent. during five months (equivalent to 14.9 per cent. per year) on the assumption that it contained the amount of "available chlorin" declared on the label.

Concentrated Solution Sodium Hypochlorite-Mulford.—This is described as a 5 per cent. aqueous solution of sodium hypochlorite containing free chlorin equivalent to from 0.2 to 1 per cent. sodium hypochlorite. It is prepared by treating a solution of sodium carbonate and sodium bicarbonate with chlorinated lime. The solution is filtered and standardized by determining the "available chlorin" and adjusting it to contain the equivalent of 5 per cent. of sodium hypochlorite.

It is proposed for use in the irrigation treatment of infected wounds after dilution with nine times its volume of water and the addition of a determined amount (stated on the label of each bottle) of boric acid to render it neutral to phenolphthalein. The manufacturer has found that development of a red color (due to formation of permanganate from the manganese contained in the chlorinated lime) is indicative of deterioration, and therefore warns against any solution which has become pink.

A specimen of concentrated solution of sodium hypochlorite-Mulford was sent the Council on Pharmacy and Chemistry in June, 1917, with a view of having the product admitted to New and Nonofficial Remedies. At that time it was found to contain 4.18 per cent. "available chlorin" (equivalent to 4.4 gm. sodium hypochlorite in 100 gm.). Another specimen received at the same time and kept unopened in a dark place, was examined in September, 1918, and was found to contain 2.88 per cent. available chlorin (equivalent to 3 gm. sodium hypochlorite per 100 gm.). On the assumption that the second specimen contained, at the time of its receipt, the amount of "available chlorin" found in the first, this second specimen lost 31 per cent. of its "available chlorin" during fifteen months.

At the time the specimens were received from the Mulford Company, the firm reported experiments which were under way to determine the keeping qualities of the solution. These experiments indicated marked deterioration of the specimens, which had become red from permanganate formation, and also that one specimen, which had not become red, had lost 5 per cent. of its available chlorin in one month. The Mulford Company explained that when sufficient data had been accumulated, a decision would be made either as to placing a time limit on the solution or making a claim as to the rate of deterioration. When the extreme deterioration found by this Laboratory was reported to the Mulford Company, the firm replied that this was a much greater loss than the average deterioration found in its chemical laboratory, namely, an average of 10 or 12 per cent. per year. It advised that because of the instability of concentrated solution of sodium hypochlorite, its manufacture had been discontinued.

HALE'S EPILEPTIC RELIEF

One bottle (with original label removed) labeled "Hale's Epileptic Relief," was submitted to the Chemical Laboratory for an estimation of the bromid content. The bottle contained about 120 c.c. (4 fluidounces) of a brown colored fluid, having an aromatic odor and a salty taste. Qualitative tests showed the presence of ammonium, potassium, sodium and bromid. Iodids were not found. Calculating from the quantitative haloid determinations, 100 c.c. of the liquid contains bromid equivalent to 20.73 gm. of potassium bromid. Therefore, each teaspoonful (4 c.c.—one dose) contains essentially 13 grains of potassium bromid, and each daily dose (4 teaspoonfuls) is equivalent to 52 grains of potassium bromid.

Accompanying the bottle was a small package of laxative pills. These were found to contain emodin-bearing drugs—possibly aloes.

IODINIZED EMULSION (SCOTT)

Iodinized Emulsion (Scott) was submitted to the Council on Pharmacy and Chemistry by the Dawson Pharmacal Company, Dawson Springs, Ky. The label declared that "Each fluidram contains: Alcohol, m. 4¾; Rectified Ol. of Turpentine, m. 3½; Iodine, gr. ⅛; Phenol, gr. ½; Glycerine and Elixir Lactated Pepsin with Aromatic Oils in the form of a perfect emulsion." A circular, which gives what was asserted to be the composition of Iodinized Emulsion (Scott) declared that, among other ingredients, each fluidram contains "one and three-quarters m. Tincture of Iodine."

The following tests demonstrated that the preparation contained no free iodin, but an iodid instead:

(*a*) Ten c.c. of the Iodinized Emulsion were shaken with 5 c.c. of chloroform. The chloroformic layer remained colorless. This indicated the absence of free iodin.

(*b*) Ten c.c. of the product, after acidification and addition of chloramine-T, was shaken with 5 c.c. of chloroform. A violet color was imparted to the chloroformic layer indicating the presence of iodid.

Besides other objections which made it unacceptable, the Council held that the composition of Iodinized Emulsion (Scott) was incorrectly declared as regards the presence of free iodin. It held that both the statement on the label that the preparation contains "iodin" and the one in the circular that "tincture of iodine" is present in the product, are incorrect.

PHENETIDYL-ACETPHENETIDIN HYDROCHLORID

(Holocain Hydrochlorid)

Phenetidyl-acetphenetidin hydrochlorid was originally submitted to the Council by Farbwerke, vorm Meister, Lucius and Bruening, Hoechst A. M., Germany, and the original description appearing in the first edition (1907) of New and Nonofficial Remedies, has been continued in the subsequent editions.

In the past the phenetidyl-acetphenetidin hydrochlorid marketed in the United States has been the product of the German manufacturers, although apparently there was no U. S. patent, and the German patents on it (Nos. 79,868 and 80,568) had expired. After the Federal Trade Commission began to issue licenses to American manufacturers to make products the supply of which had been cut off on account of the war, some firms in the United States undertook to manufacture phentidyl-acetphenetidin hydrochlorid. The Committee on Synthetic Drugs of the National Research Council, desiring that the consumer be assured that the synthetic drugs made in the United States were satisfactory, asked the Chemical Laboratory of the A. M. A. to examine samples submitted by prospective manufacturers and pass judgment as to their quality. The Synthetic Products Co. of St. Louis, and the John T. Milliken Co. of St. Louis submitted samples to the Committee on Synthetic Drugs. Later on the H. A. Metz Laboratories, Inc., New York, sent a specimen directly to the Council. All these were examined and compared with an original sample of the Farbwerke-Hoechst Co, still in possession of the Laboratory.

As the description in New and Nonofficial Remedies under holocain hydrochlorid was inadequate for the control of the drug, a study of it was made with the view of fixing proper standards of purity and strength.

In New and Nonofficial Remedies[1] it is stated that phenetidyl-acetphenetidin hydrochlorid is "ethenyl-paradiethoxydiphenyl-amidin hydrochloride," and has the formula, "$CH_3C:(NC_6H_4OC_2H_5)(NHC_6H_4OC_2H_5).HCl$." It is also stated that it "is prepared by the interaction of molecular proportions of paraphenetidin sulphate and acetphenetidin (phenacetin) in the presence of phosphorus oxychlorid, decomposing the resulting holocain sulphate with sodium hydroxid, crystallizing the base from alcohol, neutralizing it with hydrochloric acid and cystallizing."

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[1] N. N. R.: 1918, p. 259.

Phenetidyl-acetphenetidin hydrochlorid is described in New and Nonofficial Remedies as occurring in the form of small colorless crystals, neutral or faintly alkaline, odorless, faintly bitter, and producing transient numbness on the tongue.

Melting points for both phenetidyl-acetphenteidin hydrochlorid and the free base are given in New and Nonofficial Remedies; also a statement as to solubility. Since it is the salt of a weak base, the base is set free and precipitates on the addition of ammonia water, and New and Nonofficial Remedies mentions this, as well as the fact that silver nitrate gives a precipitate in solutions of it. It is also stated in this book that no weighable ash should be left on ignition. Beyond this, no standards or requirements are made.

From the foregoing it seemed desirable to investigate the following points: Melting point, solubility, per cent. of free base, purity of the base, the presence of phenetidin, and of phosphorous compounds, moisture and ash. It was also deemed desirable to prepare the platinum salt as a means of checking the constitution of the substance.

Moisture.—In the course of the examination of the various specimens it was found that they all contained moisture, and it was then seen to be important to establish a limit of moisture. Some experiments were tried to determine the necessary amount of heat to bring the hydrochlorid to constant weight. Drying in a desiccator was first tried because of the possible loss of hydrogen chlorid at high temperature: 2.0692 gm. of a specimen were placed in a desiccator over sulphuric acid, and after about fifty-six hours it had ceased to lose weight. The total loss was 0.0465 gm., or 2.25 per cent. On drying two hours at 100 C., a further loss of 0.0597 gm. was sustained. The total loss was then 0.1062 gm., or 5.13 per cent. A further drying of three hours did not change the weight.

0.646 gm. of the above dried sample was exposed in an open beaker for twenty-four hours, but did not gain in weight. Placed in a vessel and exposed to moist air for twenty-four hours, it gained 0.0347 gm., and therefore contained 5.1 per cent. moisture. In a desiccator over sulphuric acid about sixty hours the loss was but 0.0162 gm., or 2.38 per cent. Two hours in an oven at 100 C. restored it to the original weight. From this it would seem that only about 50 per cent. of the moisture was removed over sulphuric acid even in two and one-half days' time, while it was removed at 100 C. in two hours.

Farbwerke-Hoechst Co.—0.5063 gm. lost on drying for two hours at 100 C., 0.0263 gm., or 5.19 per cent.; 0.5057 gm. lost 0.0251 gm., or 4.96 per cent.; 0.5078 gm. lost 0.026 gm., or 5.12 per cent. Average, 5.09.

John T. Milliken Co.—2.0692 gm. lost on drying for two hours at 100 C., 0.1062 gm., or 5.13 per cent.

Synthetic Products Co.—0.9486 gm. lost on drying for two hours at 100 C., 0.275 gm., or 2.9 per cent.

H. A. Metz Laboratories, Inc.—2.0000 gm. lost on drying for two hours at 100 C., 0.0997 gm., or 4.99 per cent.

Melting Points of Phenetidyl-Acetphenetidin Hydrochlorid and the Base.—The German patent evidently describes the base as melting at 121 C. Kennert,[2] however, states that the melting point is 117 C. Other authorities quote these two figures, and they seem to be the origin of all the statements as to the melting point of the base.

Kennert seems to be the originator of the statement that the hydrochlorid melts at 189 C.

New and Nonofficial Remedies states that the base melts at 121 C. and the hydrochloric at 189 C. In determining the melting point of the samples of hydrochlorid, some variation was at once noticed. Also, as is usual in the case of such salts, the melting point was not as sharp as is desirable. The melting point of the various specimens, however, came within the rather narrow range of 2.5 degrees, or from 190 to 192.5. Since it is well known that when one pure substance is mixed with another substance of different constitution, even though the melting point of the two be the same, the melting point of the mixture is lower, it was decided to take advantage of this fact to establish the identity of the samples. The melting point of the specimen was taken alone and then again after being mixed with an authentic specimens. In no case was a marked difference noted.

After purification, by cystallization from hot alcohol, the base was found to melt at from 116 to 117 C. in all cases. This agrees with the statement of Kennert.

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2. Kennert: Chem. Centralbl. **2**: 556, 1897; Apoth. Ztg. **12**: 519-20, 1897.

All the results are given in the appended table.

Phosphorous Compounds.—Since phosphorous oxychlorid is used in the manufacture of phenetidyl-acetphenetidin, the presence of it or of its decomposition products in the finished product would indicate careless preparation and would also be objectionable from a therapeutic standpoint.

To economize the sample, the ammoniacal solution from which the base was extracted was used for this test. To this was added nitric acid, and then the mixture was evaporated to a small volume and added to ammonium molybdate solution and warmed. In no case was a phosphorous compound found.

Phenetidin.—While the tests for phenetidin are not very satisfactory, it was deemed advisable to include a test to avoid possible contamination or adulteration with this product. Kennert describes such a test. He states that after boiling with hydrochloric acid, phenetidin hydrochlorid is formed, which on oxidation with chromic acid gives a ruby-red color. This color reaction is also mentioned in the U. S. Pharmacopeia as a test for acetphenetidin. According to this test, none of the samples contained phenetidin. The test was found to be rather unsatisfactory, since as much as 4.5 per cent. phenacetin could be added to phenetidyl-acetphenetidin hydrochlorid without producing a distinctive coloration.

Color Reactions.—Kennert describes a color reaction with chlorinated soda which he asserts distinguishes phenetidyl-acetphenetidin from cocain and eucain. This consists in treating a solution of the hydrochlorid with chlorinated soda, when a flesh-colored solution is obtained from which a violet precipitate separates. This violet precipitate dissolves in ether to a Burgundy-red solution, which turns dark green after a time. This reaction is also mentioned by Rosenthaler,[3] and is said to be due to the formation of indol, analogous to the reactions obtained when anilin is oxidized with hypochlorite solution.

Ash.—Since the percentage of ash should be very slight in such products as this, its determination presented some difficulties. The test is very expensive if a quantity is used, say 1 to 2 gm., sufficiently large to reduce the experimental error to a minimum. On the other hand, if smaller quantities are used, the experimental errors, unless extreme care is taken, are liable to cause a 100 per cent. error in the determination

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[3] Rosenthaler: Der. Nach. Organ. Verbind. 748, 1914.

It was found that by working carefully with a platinum crucible, heating always the same length of time, cooling the same length of time, etc., very good duplicate determinations could be made with as little as 0.300 gm. of the hydrochlorid.

FARBWERKE-HOECHST CO.—0.3586 gm. gave 0.0006 gm. residue, or 0.167 per cent.; 0.3105 gm. gave 0.0005 gm. residue, or 0.16 per cent. Average, 0.164 per cent.

JOHN T. MILLIKEN CO.—0.3000 gm. gave no ash. A duplicate gave the same result.

SYNTHETIC PRODUCTS CO.—0.3000 gm. gave 0.0004 gm. residue, or 0.13 per cent. A duplicate gave the same result.

H. A. METZ LABORATORIES, INC.—0.3552 gm. gave no residue. A duplicate gave the same result.

Solubility.—Täuber[4] asserts that the hydrochlorid dissolves in boiling water up to 11 per cent. and in cold water up to 2.5 per cent. This would be 1 gm. in 40 c.c. water. Other authorities quote this statement. In New and Nonofficial Remedies it is stated that it dissolves in 50 parts of water. In a letter from the H. A. Metz Laboratories, Inc., it was stated that their product dissolved 1 in 50 parts of water at 50 C. and did not crystallize on cooling.

Kennert states that the base dissolves 1 in 2.218 of water at 15 C.

These statements were not verified by accurate determinations. In a general way they seemed to be correct.

Per Cent. of Base.—From the formula already given, the theoretical per cent. of base is 89.1. It may be determined by adding ammonia water to the solution in water of a weighed quantity, extracting the liberated base with chloroform, evaporating the chloroform carefully, drying the base at 100 C. and weighing.

Since but small quantities of the material were available, as little as possible was consumed in the analysis. After a few trials 0.5 gm. seemed ample for this test, and the separated base could be used for other tests as indicated further on in this article.

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[4] Täuber: Chem. Centralbl. **1**: 1100, 1897; Therap. Monatsh. **11**: 216-17 (April) 1897.

The following publications were also consulted:

Gutmann: Chem. Centralbl. **1**:875, 1897; Deutsch. med. Wchnschr. **11**: 165-67, 1897.

Schmidt: Pharm. Chem. **2**: 990.

Beilstein: **2**: 403.

Arend: Neue Arznei n. spev. Ed. **4**: 271, 1913.

Hankin: Chem. Abstr. **1**: 524, 1917; Indian J. M. Res. **4**: 247, 1916.

Hankin: Chem. Abstr. **1**: 2145, 1911.

Farbwerke-Hoechst Co.—0.4806 gm. hydrochlorid gave 0.4311 gm. base, or 89.69 per cent.; 0.5078 gm. gave 0.43200 gm., or 89.62 per cent. base. Average, 89.65 per cent. On titration the 0.432 gm. of base required 14.49 c.c. tenth-normal acid, indicating 0.4321 gm. base, or 100 per cent. pure, or 89.64 per cent. base in the hydrochlorid.

John T. Milliken Co.—0.548 gm hydrochlorid gave 0.4885 gm. base, or 89.16 per cent. On titration the 0.4885 gm. required 9.06 c.c. tenth-normal acid, indicating 0.48845 gm. base, or 100 per cent. pure, or 89.16 base in the hydrochlorid.

Synthetic Products Co.—0.5755 gm. of the hydrochlorid gave 0.5119 gm. of base, or 87.49 per cent. On titration this required 16.84 c.c. tenth-normal acid, indicating 0.5022 gm. base, or 98.1 per cent. pure, or 87.26 per cent. of the hydrochlorid.

H. A. Metz Laboratories, Inc.—0.642 gm. hydrochlorid gave 0.5729 gm. base, or 89.2 per cent. On titration this required 19.08 c.c. tenth-normal acid, indicating 0.56896 gm. base, or 99.32 per cent. pure, or 88.6 per cent. of the hydrochlorid. 0.4882 gm. hydrochlorid gave 0.4351 gm. base, or 89.08 per cent. On titration this required 14.49 c.c. tenth-normal acid, indicating 0.4321 gm. base, or 99.4 per cent. pure, or 88.51 per cent. of the hydrochlorid. Average per cent. by weight, 89.14; by titration, 88.55.

Platinum Compound.—If a platinum compound of the base is formed it would naturally be composed of two molecules of the base and one of H_2PtCl_6. The platinum compound would then contain 18.4 per cent. platinum, and each gm. would be equivalent to 0.5927 gm. of the base, and 0.6652 gm. of the hydrochlorid. In some cases this was determined on a portion of the original hydrochlorid. In other cases the base obtained in the determination of per cent. of free base was used. This latter procedure was found entirely satisfactory and resulted in considerable economy of sample.

Farbwerke-Hoechst Co.—0.3523 gm. of the hydrochlorid gave 0.5306 gm. of the platinum compound, indicating 0.3529 gm., or 100.02 per cent. pure. On ignition 0.1008 gm. platinum was obtained, or 19 per cent.

John T. Milliken Co.—0.2493 gm. of the purified base, equivalent to 0.2798 gm. of chlorid, gave 0.4154 gm. of the platinum compound, indicating 0.2766 gm., or 98.86 per cent. On ignition 0.079 gm. platinum was obtained, or 19.02 per cent.

Synthetic Products Co.—0.3128 gm. of the hydrochlorid gave 0.4562 gm. of the platinum compound, indicating

DATA OF TESTS

Manufacturer	Appearance	Moisture	Melting Point	Phosphorous Compound	Phenetidin*	Indol Reaction	Ash	Per Cent. Base by Weight	Per Cent. Base by Titration	Per Cent. Pt. in Pt. Salt†
Farbwerke-Hoechst Co. (German specimen)	Slightly pink crystal	5.09	190 to 191	Absent	Negative	Positive	0.16	89.65	89.64	19.00
John T. Milliken Co.	White crystalline powd.	5.13	191.5 to 192	Absent	Negative	Positive	0.00	89.16	89.16	19.02
Synthetic Products Co.	White crystalline powd.	2.90	192 to 192.5	Absent	Negative	Positive	0.13	87.49	87.26	19.3
H. A. Metz. Lab. Inc.	White crystalline powd.	4.99	192 to 192.5	Absent	Negative	Positive	0.00	89.14	88.55	19.34

* The phenetidin test is not very sensitive.

† The theory is 19.4 per cent.

0.3035 gm., or 97.03 per cent. pure. On ignition 0.088 gm. platinum was obtained, or 19.3 per cent.

H. A. METZ LABORATORIES, INC. 0.543 gm. of the hydrochlorid gave 0.8151 gm. of the platinum compound, indicating 0.5422 gm., or 99.85 per cent. pure. On ignition 0.1577 gm. platinum was obtained, or 19.34 per cent.

All the foregoing data is condensed in the accompanying table. All figures are based on the anhydrous material.

As a result of these experiments the following monogram was drawn up:

> *Phenetidyl-Acetphenetidin Hydrochlorid.* — Phenetidyl-acetphenetidin hydrochlorid is prepared by the interaction of molecular proportions of paraphenetidin sulphate, and acetphenetidin (phenacetin) in the presence of phosphorus oxy-chlorid. The resulting sulphate is decomposed with sodium hydroxid and the free base obtained is recrystallized from hot alcohol, neutralized with hydrochloric acid, and the hydrochlorid crystallized.
>
> Phenetidyl-acetphenetidin hydrochlorid is either a white, crystalline powder, or colorless crystals. It is odorless, and produces numbness when a small amount is placed on the tongue. It is slightly soluble in water (difference from cocain hydrochlorid and procain) and freely soluble in alcohol.
>
> Phenetidyl-acetphenetidin hydrochlorid when dried to constant weight at from 100 to 105 C. melts not lower than 189 C. When mixed with an authentic specimen of phenetidyl-acetphenetidin hydrochlorid, the melting point of the mixture should be not lower than the lowest melting temperature of either the authentic specimen or the sample under examination.
>
> In solutions of phenetidyl-acetphenetidlin hydrochlorid, alkali produces a white precipitate, iodin solution a reddish-brown precipitate, potassium mercuric iodid solution a white precipitate, and phosphomolybdic acid a white precipitate.
>
> The addition of a few drops of chlorinated soda solution to a saturated aqueous solution of phenetidyl-acetphenetidin hydrochlorid produces a finely divided flesh-colored precipitate, which remains in suspension. In a few minutes this separates as a violet-colored precipitate, and when the mixture is shaken with ether, the layer of ether is colored Burgundy-red.
>
> Dissolve about 0.05 gm. phenetidyl-acetphenetidin hydrochlorid in 2 c.c. of concentrated hydrochloric acid, boil for two or three minutes, cool, and add 1 drop potassium dichromate test solution. No ruby-red color is produced (absence of 5 per cent. or more of acetphenetidin or paraphenetidin).
>
> To about 25 c.c. water and 5 c.c. ammonia water contained in a separator, add about 0.500 gm., accurately weighed, of phenetidyl-acetphenetidin hydrochlorid which has previously been dried to constant weight at 100 to 105 C. Extract the free base by shaking out with 20, 10, 10, 10, c.c. portions of chloroform. (Preserve the solution in the separator for the test of phosphorous compounds given below.) Collect the chloroformic solutions in a beaker by passing them through a small funnel holding a pledget of cotton. Evaporate the chloroform and dry the free base at 100 to 105 C. to constant weight. The weight obtained should be not less than 87.5 or more than 90.5 per cent. of the phenetidyl-acetphenetidin hydrochlorid.
>
> Dissolve the free base obtained as described in neutral alcohol, add an excess of tenth-normal acid volumetric solution and titrate the excess with tenth-normal fixed alkali volumetric solution, using cochineal as an indicator. The titration should show the base to be not less than 98.5 per cent. pure. Each c.c. of tenth-normal acid neutralized is equivalent to 0.02981 gm. of the base.

Transfer the solution obtained in the above titration to a separator and add 5 c.c. ammonia water. Again extract the free base as directed. Purify it by crystallization from hot alcohol, and, after drying to constant weight, determine its melting point. It should melt at 116 to 117 C.

To the solution remaining in the separator, after the original extraction of the base, add an equal volume of concentrated nitric acid and boil for five minutes. Evaporate this solution to about 25 c.c. and add to it 25 c.c. ammonium molybdate test solution. Keep the mixture at a temperature of about 60 C. for three hours. No yellow precipitate is produced (phosphorus compounds).

Incinerate 0.5 gm. of phenetidyl-acetphenetidin hydrochlorid Not more than 0.1 per cent. of ash remains.

Phenetidyl-acetphenetidin hydrochlorid when dried to constant weight at 100 to 105 C. does not lose more than 5 per cent. of its weight.

If boiled in glass vessels the aqueous solution of phenetidyl-acetphenetidin hydrochlorid may become turbid. This is due to a separation of a small quantity for the free base by the action of the alkali dissolved from the glass. For this reason glass vessels should be avoided, porcelain being used instead.

RHEUMATISM TREATMENT

A request was received for the examination of a rheumatism treatment said to be exploited by a physician in California. The correspondent stated that it was administered per rectum and that $150 to $500 is charged for the treatment. The correspondent further stated that an attempt was being made to raise funds for a large sanatorium in connection with the treatment, and hence an examination of the preparation was deemed advisable.

Four specimens were received, two said to be diluted with water, and two specimens (about 5 c.c. each) said to be undiluted.

All the bottles contained a pink liquid. The two "diluted" specimens had an odor suggestive of methyl salicylate. The two "undiluted" specimens were odorless.

Qualitative tests of all specimens indicated sodium and salicylate in considerable amounts. The presence of iodid or of colchicin could not be demonstrated.

The qualitative examination indicating the presence of sodium salicylate as the essential ingredient, the two undiluted specimens were mixed and the sodium salicylate determined. This was done by liberating the salicylic acid by addition of acid, extraction with ether and weighing and titrating the salicylic acid obtained. This determination indicated the presence of 0.1162 gm. sodium salicylate in 1 c.c., approximately equivalent to 60 grains sodium salicylate per fluidounce.

From the examination it is probable that the "rheumatism treatment" (undiluted) is essentially an aqueous solution containing about 60 grains of sodium salicylate per fluidounce.

Details of Analysis

Three c.c. of the undiluted product after acidification were extracted with four portions of ether and this evaporated. The residue was found to weigh 0.3081 gm. This was then dissolved in dilute alcohol, phenolphthalein added and titrated with tenth-normal NaOH (factor 1.012); 21.5 c.c. of tenth-normal NaOH (factor 1.012) were required, corresponding to 0.3008 gm. of salicylic acid or calculated to sodium salicylate, 0.3487 gm.

In a duplicate determination, the residue was not weighed. Its titration required 21.5 c.c. tenth-normal sodium hydroxid volumetric solution (factor 1.012).

THE STANDARDIZATION OF COMMERCIAL BISMUTH TRIBROMPHENATE

William Rabak, Ph.G., Sc.B.

This work was begun in view of a request received by the Council on Pharmacy and Chemistry from the Medical Section of the Council of National Defense for a report on the quality of bismuth tribromphenate, offered to the government by a certain firm.

In submitting a specimen of its product, "Bismuth Tribromphenolate," the firm claimed that "it is of high character, matching exactly the German product formerly imported into this country," and expressed the belief that it would be found to conform to the standards for this preparation in New and Nonofficial Remedies. Later a second specimen was received from the same company, with the request that this be substituted for that first received. It was explained that the first had been taken from an experimental lot, and that the second, taken from the regular factory output, was identical with the first except that it was free from odor because of the more thorough washing to which it had been subjected. Accordingly, the examination which is reported below refers to the second specimen only.

New and Nonofficial Remedies, 1918, defines bismuth tribromphenate as basis bismuth tribromphenate having the formula $Bi(C_6H_2Br_3O)_2OH.Bi_2O_3$, and it is required to yield not less than 49.5 per cent. of bismuth oxid (the chemical formula requires 46.2 per cent. bismuth, or 51.6 per cent. bismuth oxid, Bi_2O_3, and 49.2 per cent. tribromphenate, $C_6H_2Br_3.OH$). It describes it as a "fine, yellow, nearly odorless and tasteless powder, neutral in reaction," and "only slightly soluble in water, alcohol, chloroform, liquid petrolatum and vegetable oils." It is required to yield tribromphenol (to which a melting point of 95 C. is assigned) when decomposed by alkali and the alkali tribromphenate decomposed by acid, the separated tribromphenol purified and dried.

As the New and Nonofficial Remedies description appeared loosely drawn—it had been based on information furnished for the product Xeroform when this, because of patent protection, was the only bismuth tribromphenate on the market—it was decided to include in the examination also specimens of the two brands of Bismuth Tribromphenate included in New and Nonofficial Remedies, namely, Bismuth Tribromphenate-Merck (Merck and Company) and Xeroform-Heyden (The Heyden Chemical Works). The Merck specimen had been received by the Council from Merck and Company in 1915, while the Heyden preparation was obtained direct from the firm's Chicago branch in April, 1918. At this time Bismuth Tribromphenate-Merck could not be obtained from the Chicago wholesale houses.

All three specimens were nearly odorless. Two of the specimens (the Research Council Specimen and Merck products) were of a lemon-yellow color, while the Heyden preparation was of a grayish color.

BISMUTH DETERMINATION

Four methods for the determination of the bismuth content of the specimens were tried:

(*A*). *Direct ignition to bismuth oxid.*—This method was abandoned because of the tendency to ignite suddenly during the incineration and the consequent loss of material.

(B). The method of the Japanese Pharmacopoeia Third Revised Edition, translated by the Pharmaceutical Society of Japan).—The method consists in treatment of the product with nitric acid, evaporation and subsequent heating to bismuth oxid. This method also was abandoned because of tendency toward sudden ignition with loss of material.

(*C*). *The method of Kollo (Apotheker Zeitung, 1910, p. 99).*—The method consists in decomposition of the product by heating on water bath with normal sodium hydroxid solution, with formation of soluble sodium tribromphenate and insoluble bismuth hydroxid. The bismuth hydroxid is collected on a filter, washed with hot water until a few drops of the filtrate no longer turn litmus paper blue, dried and heated to constant weight and weighed as bismuth oxid.

(*D*). *A. M. A. Method (Reports A. M. A. Chem. Lab., 1911, p. 18).*—This method consists in dissolving the product in hot, strong hydrochloric acid, diluting, filtering and precipitating by saturation with hydrogen sulphid. The bismuth sulphid obtained is dissolved in nitric acid and from the solution obtained the bismuth is precipitated by addition of an excess of ammonium hydroxid and ammonium carbonate. The precipitate is collected and converted to bismuth oxid by heat.

The following tabulation shows the results obtained by Methods "C" and "D":

TABLE 1.—BISMUTH CONTENT OF BISMUTH TRIBROMPHENATE

	Method	Gm. of Salt	Gm. of Bi_2O_3	Per Cent. of Bi_2O_3
No. 1 Research Council Spec.	C	2.1312	1.1754	55.1
No. 1 Research Council Spec.	D	0.5151	0.2772	50.03
No. 2 (Merck and Company)	C	2.0287	1.2543	61.8
No. 2 (Merck and Company)	D	0.5064	0.2634	52.01
No. 3 (Heyden Chem. Works)	C	2.0472	1.6020	78.2
No. 3 (Heyden Chem. Works)	D	0.5227	0.3546	67.8

It is seen from the tabulation that the results obtained by the Kollo method (Method C) are higher than those by the sulphid method (Method D) and that duplicate determinations show a rather wide variation. The results by the sulphid method are somewhat lower than those by the Kollo method, but duplicates agree fairly well. In view of the fact that the Kollo method will give excessive results if impurities such as talcum, etc., are present and in consideration of the satisfactory results obtained in previous work with the sulphid method, the figures obtained by this method are taken as indicative of the bismuth content of the specimens examined. Calculating the per cent. of bismuth oxid obtained to bismuth (Bi), the following values are obtained:

Bismuth Tribromphenolate, Research Council Specimen: Bismuth 44.8 per cent.

Bismuth Tribromphenate-Merck, Merck and Co.: Bismuth 46.6 per cent.

Xeroform, Heyden Chemical Works: Bismuth 60.7 per cent.

TOTAL TRIBROMPHENOL

The content of tribromphenate radicle, $C_6H_2Br_3O^-$, was determined by the method of Kollo (Apotheker Zeitung, 1910, p. 99). It consists in titrating the filtrate of the bismuth oxid determination of Kollo, described under "C" (bismuth determinations), with normal hydrochloric acid, using phenolphthalein as an indicator. The cubic centimeters of normal alkali consumed multiplied by the theoretical factor 0.331 gives the weight of tribromphenol (combined and free) contained in the specimen.

The following results were obtained:

TABLE 2.—DETERMINATION OF TOTAL TRIBROMPHENOL IN BISMUTH TRIBROMPHENATE

	Gm. of Salt Taken	Gm. Tribromphenol Calculated from Theoretical Factor	Per Cent. of Total Tribromphenol
No. 1 (Research Council Spec.)	1.7817	1.0592	59.44
No. 2 (Merck and Company)...	0.9743	0.5627	57.75
No. 3 (Heyden Chem. Works)..	2.0440	0.4303	21.04

UNCOMBINED TRIBROMPHENOL

The definite chemical formula given in New and Nonofficial Remedies for bismuth tribromphenate and the statement that it is "only slightly soluble in . . . alcohol . . ." requires the absence of uncombined tribromphenol, but no method for its detection or determination is provided.

In the U. S. Patent 516,358 (expired March 13, 1911), issued to Bruno Richard Seifert, assignor to Dr. F. Von Heyden, for "Phenol Bismuth Compound" the freedom from uncombined tribromphenol was provided for by the direction to wash with alcohol the product obtained.

In the Swiss Pharmacopoeia the permissible content of uncombined tribromphenol is limited thus:

> "If 0.5 gm. be shaken with 5 c.c. of alcohol and 1 c.c. of the filtrate be diluted with 15 c.c. of water, neither a turbidity nor a flocculent precipitate should appear . . ."

When this test was applied to the three specimens under examination, the Merck and Heyden specimens complied, while the Research Council specimen did not comply, with this requirement.

Method 1.—About 1 gm. of bismuth tribromphenate was placed in a flask, 20 c c of 95 per cent. alcohol added and shaken for fifteen minutes, after which it was filtered by suction through a Gooch filter into an Erlenmeyer flask. The flask was rinsed with 10 c.c. of alcohol and finally the filter was washed with 10 c.c. of alcohol, 25 c.c. of tenth-normal sodium hydroxid solution were added to the alcoholic filtrate (which was nearly but not perfectly clear) containing the tribromphenol, and the residual alkali titrated with tenth-normal hydrochloric acid.

The number of cubic centimeters of tenth-normal alkali consumed multiplied by 0.331 gave the weight of tribromphenol (Table 3).

TABLE 3.—DETERMINATION OF FREE TRIBROMPHENOL

	Gm. of Salt Taken	Gm. Tribromphenol Calculated from Theoretical Factor	Per Cent. Free Tribromphenol
Research Council Spec.	2.3351	0.3806	16.31
Merck and Company	0.7980	0.0364	4.56
Heyden Chemical Works	1.9460	0.0132	0.68

Method 2.—About 2 gm. of bismuth tribromphenate were placed in a glass stoppered Erlenmeyer flask, 100 c.c. of alcohol were measured in and shaken during one-half hour and allowed to stand over night. Fifty c.c. of the supernatant liquid were then removed by means of a pipet, a slight excess of tenth-normal sodium hydroxid added and the residual alkali titrated with tenth-normal HCl.

Table 4 gives results obtained.

TABLE 4.—PER CENT. OF TRIBROMPHENOL BY METHOD 2

	Gm. of Salt Taken	Gm. Tribromphenol Calculated from Theoretical Factor	Per Cent. Free Tribromphenol
Research Council Spec.	2.0712	0.3905	18.85
Merck and Company	1.9417	0.0760	3.92
Heyden Chemical Works	2.0440	0.0198	0.97

Table 5 gives a comparison of the results obtained by the two methods.

TABLE 5.—COMPARISON OF RESULTS BY METHODS 1 AND 2

	Method 1	Method 2
Research Council Spec.	16.31	18.85
Merck and Company	4.56	3.92
Heyden Chemical Works	0.68	0.97

The results obtained in Method 1 (the percolation method) apparently are reliable and, as the method is the more simple, may be given preference.

COMBINED TRIBROMPHENOL (TRIBROMPHENATE)

The amount of tribromphenol existing in the specimen in combination was calculated by subtracting from the per cent. of total tribromphenol determined, the per cent. of free tribromphenol found by Method 1.

The figures obtained are given in Table 6.

TABLE 6.—THE TRIBROMPHENATE CONTENT OF BISMUTH TRIBROMPHENATE

	Per Cent. of Combined Tribromphenol
Research Council Specimen	43.13
Merck and Company	53.19
Heyden Chemical Works	20.36

SUMMARY

From the foregoing the specimens examined contain the percentages shown in Table 7 of bismuth (Bi), combined tribromphenate and free tribromphenol.

TABLE 7.—PERCENTAGES OF BISMUTH AND OF COMBINED TRIBROMPHENATE AND FREE TRIBROMPHENOL

	Per Cent. Bismuth	Per Cent. Combined Tribromphenol	Per Cent. Free Tribromphenol
Research Council Spec.	44.8	43.13	16.31
Merck and Company	46.6	53.19	4.56
Heyden Chemical Works	60.7	20.36	0.68

This examination shows:

1. The Bismuth Tribromphenolate submitted to the Council of National Defense, does not correspond to the description of bismuth tribromphenate in New and Nonofficial Remedies.
2. As now supplied, Xeroform-Heyden does not meet the requirements for bismuth tribromphenate, nor does its composition correspond to that of the product formerly supplied.
3. The description in New and Nonofficial Remedies of bismuth tribromphenate should provide an upper, as well as a lower, limit for the bismuth content; it should provide tests for the absence of adulterants, and also set a limit of permissible uncombined tribromphenol.

Report to Council of National Defense

The results of this examination with reference to the Research Council specimen having been submitted to the Council on Pharmacy and Chemistry, this body advised the Medical Section of the Council of National Defense as follows:

1. The specimen of "Bismuth Tribromphenolate" sent to the Council of National Defense complies with the New and Nonofficial Remedies description for bismuth tribromphenate, except that it contains considerable amounts (approximately 16 per cent.) of alcohol-soluble, uncombined tribromphenol.

Revision of N. N. R. Standards

The results of the examination of the three specimens were sent to the Heyden Chemical Works and to Merck and Co. (in each case disclosing the identity of the particular firm's product), asking aid in the standardization of the product. After Merck and Co. had submitted valuable advice for a revision of the somewhat loosely drawn standards for bismuth tribromphenate in N. N. R. 1918, the inquiry whether the following proposed revision of the description of bismuth tribromphenate in New and Nonofficial Remedies was acceptable, was submitted to both firms:

BISMUTH TRIBROMPHENATE.—Bismuthi Tribromphenas.—Bismuth Tribromphenol.—Xeroform.—A basic bismuth tribromphenate of variable composition.

An amorphous, yellow, nearly odorless and tasteless powder, neutral to moistened litmus paper.

It is only slightly soluble in water, alcohol, chloroform, liquid petrolatum and vegetable oils. Alkalies and strong acids decompose it. It is stable at temperatures below 120 C.

When about 1 gm. of the salt is boiled with 10 c.c. of sodium hydroxide test solution, the liquid filtered, and the filtrate acidulated with sulphuric acid, the white curdy precipitate produced, when washed and dried, melts at 90 to 95 C. (*tribromphenol*). The contents of the filter dissolve completely in dilute hydrochloric acid (insoluble *inert material*).

Boil 1 gm. of bismuth tribromphenate with 20 c.c. of a mixture of equal parts of acetic acid and distilled water, cool the solution and filter. Free the filtrate from bismuth by the addition of hydrogen sulphide, boil the mixture and again filter. The latter filtrate leaves not more than 0.005 gm. of residue on evaporation and gentle ignition (*alkalies and alkali earths*).

Shake for one minute in a separatory funnel, 2 gm. of bismuth tribromphenate, 20 c.c. of ether, and 20 c.c. of a mixture of equal volumes of hydrochloric acid and distilled water. Draw off the aqueous portion and concentrate to about 4 c.c.; pour it into 100 c.c. distilled water, filter, evaporate the filtrate on the water bath to 30 c.c., again filter and divide this filtrate into portions of 5 c.c. each. Mix one portion with an equal volume of dilute sulphuric acid; it does not become cloudy (*lead*). Treat another portion with a slight excess of ammonia water; the supernatant liquid does not exhibit a bluish tint (*copper*). Another portion is not immediately affected by barium nitrate test solution (*sulphate*).

Heat gently a mixture of about 0.2 gm. of bismuth tribromphenate with 5 c.c. of potassium hydroxide test solution and about 0.2 gm. of aluminum wire; the vapors evolved do not turn red litmus blue (*nitrates*).

Shake 1 gm. of bismuth tribromphenate frequently during fifteen minutes with 30 c.c. of alcohol (95 per cent.) filter and rinse flask with two separate 10 c.c. portions of alcohol, allowing the washings to run through filter. To the combined filtrate and washings add 20 c.c.

of tenth-normal sodium hydroxide and a few drops of phenolphthalein solution and determine the excess of alkali with tenth-normal hydrochloric acid. Not more than 1 c.c. of tenth-normal sodium hydroxide should have been consumed by the alcoholic liquid (*free tribromphenol*).

Add 2 c.c. of nitric acid to 2 gm. of bismuth tribromphenate in a porcelain crucible, carefully evaporate to dryness on a sand bath and incinerate. Dissolve the residue in 5 c.c. of concentrated hydrochloric acid and add to the solution 10 c.c. of a saturated solution of stannous chloride in concentrated hydrochloric acid. The mixture should not darken on standing thirty minutes (*arsenic*).

Mix 0.5 gm. of the salt with 10 c.c. of a mixture of equal parts of hydrochloric acid, U. S. P. and distilled water. No effervescence should occur (*carbonate*).

To about 0.5 gm. of bismuth tribromphenate, accurately weighed, add 20 c.c. of hydrochloric acid and digest on water bath. Add 150 c.c. of distilled water and filter. Rinse the beaker with 30 c.c. of distilled water and allow the washings to run through the filter. Saturate the combined filtrate and washings with hydrogen sulphide, filter off the bismuth sulphide, wash and dissolve in hot dilute ntric acid. Add a slight excess of ammonia water followed by 2 c.c. of ammonium carbonate test solution. Allow to stand thirty minutes, filter off the precipitated bismuth hydroxide and heat to constant weight at dull red heat. The residue of bismuth oxide (Bi_2O_3) should be not less than 45 per cent. nor more than 55 per cent. of the original weight of bismuth tribromphenate taken, corresponding to not less than 40 per cent. nor more thain 49 per cent. of bismuth.

The Heyden Chemical Works accepted the proposed monograph. Regarding the Laboratory's findings, the firm stated that "the product had to be made in this country after importations from Europe became impossible and the first lots were not fully up to the standard." Later the firm stated that it could furnish a product which it considered equal to that which was previously imported and offered to submit "samples of the new material."

Merck and Co. acknowledged the receipt of the monograph but made no statement as to its acceptance or suggestions for its revision. As the new monograph was accepted by the Heyden Chemical Works and as Merck and Co. offered no objections, it was adopted for N. N. R., 1919, by the Council on Pharmacy and Chemistry.

In November, 1918, Merck and Co. sent a specimen labeled "Bismuth Tribromphenate-Merck," "Merck and Co., New York, Distributors and Guarantors" and wrote: "You will notice this sample conforms in nearly all details to the tests submitted with our letter of June 4. We have been able to produce better goods, but just at present unsatisfactory starting material confronts us."

Examination of the specimen demonstrated that it was soluble to a considerable extent in alcohol (the N. N. R., 1918, description provides that it should be only slightly soluble in alcohol) and, according to the standards adopted for New and Nonofficial Remedies, 1919, contained 18 per cent. of uncombined tribromphenol (more than five times the permitted amount).

In December, 1918, Merck and Co. submitted another specimen and said: "We believe this is a better grade than we have been able to make in the recent past. It seems to meet all the tests for N. N. R., 1919, with two exceptions: these are (*a*) solubility in alcohol, and (*b*) the test for uncombined tribromphenol."

When the two recent samples of bismuth tribromphenate-Merck and two samples of Xeroform-Heyden were examined according to the new monograph the results given in Table 8 were obtained.

TABLE 8.—EXAMINATION OF TRIBROMPHENATE AND XEROFORM

1. BISMUTH.

Brand and Date Received	Weight Taken Gm.	Weight of Bi_2O_3 Obtained Gm.	Per Cent. of Bismuth Gm.
Xeroform-Heyden (from mfr.) July, 1918	0.6754	0.3565	47.2
Xeroform-Heyden (open market) July, 1918	0.8259	0.6156	66.7
Bismuth tribromphenate-Merck Nov., 1918	0.4882	0.2512	46.1
Bismuth tribromphenate-Merck Dec., 1918	0.8869	0.4495	45.5

2. UNCOMBINED TRIBROMPHENOL.

Brand and Date Received	Weight Taken Gm.	No. Cc. of Tenth-Normal NaOH Consumed, C.c.	Per Cent. of Free Tribromphenol
Xeroform-Heyden (from mfr) July, 1918	1	7.4	24.5
Xeroform-Heyden (open market) July, 1918	1	0.7	2.3
Bismuth Tribromphenate-Merck Nov., 1918	1	5.7	18.8
Bismuth Tribromphenate-Merck Dec., 1918	1	5	16.5

In view of the Labortory's report the referee of the Council on Pharmacy and Chemistry in charge of bismuth tribromphenate recommended that the acceptance of Xeroform-Heyden and bismuth tribromphenate-Merck be withdrawn, but that this should be without prejudice to their reinstatement when satisfactory products are again offered for sale. The Council adopted the recommendation of the referee and accordingly Xeroform-Heyden and bismuth tribromphenate-Merck are omitted from New and Nonofficial Remedies, 1919.

When the Laboratory's findings with regard to Xeroform-Heyden and the action of the Council deleting the article from New and Nonofficial Remedies was reported to the Heyden Chemical Works, the firm expressed regret that efforts to produce a product equal to that formerly obtained from Germany had so far not been successful and announced that it had decided to withdraw Xeroform-Heyden from the market for the present. When Merck and Co. was advised in regard to the report of the Laboratory and Council's action, this firm questioned the feasibility of producing a product meeting the Council's standards and suggested that the test for free tribromphenol be revised to permit as much as 15 per cent. of this constituent. When Merck and Co. was reminded that its product submitted in 1915 essentially complied with the adopted standards (an old sample of Xeroform-Heyden was also found to comply) and that the estimate of the therapeutic value of bismuth tribromphenate is based on a product essentially devoid of free tribromphenol, the firm replied:

> "As stated in our letter of the 12th inst., we do not wish to market the chemical unless it meets all legitimate requirements of the physicians that use it. If, therefore, your standard proves to be good and it is commercially possible to make supplies conforming to it, we shall do so. We shall discontinue the article unless it is of suitable quality."

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